Supplement B The Chemistry of Acid Derivatives
Edited by Saul Patai

Supplement B

The chemistry of **acid derivatives** Part 1

Edited by
SAUL PATAI
The Hebrew University, Jerusalem

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Foreword

Most of the originally planned volumes of the series *The Chemistry of the Functional Groups* have appeared already or are in the press. The first two books of the series, *The Chemistry of Alkenes* (1964) and *The Chemistry of the Carbonyl Group* (1966) each had a second volume published in 1970, with chapters not included in the plans of the original volumes and others which were planned but failed to materialize.

This book is the second of a set of supplementary volumes which should include material on more than a single functional group. For these volumes a division into six categories is envisaged, and supplementary volumes in each of these categories will be published as the need arises. These volumes should include 'missing chapters' as well as chapters which give a unified and comparative treatment of several related functional groups together.

The planned division is as follows:

Supplement A: The Chemistry of Double-Bonded Functional Groups (C=C; C=O; C=N; N=N etc.).

SupplementB: The Chemistry of Acid Derivatives (COOH; COOR; $CONH_2$ etc.).

Supplement C: The Chemistry of Triple-Bonded Functional Groups (C≡C; C≡N; $-\overset{+}{N}\equiv N$ etc.).

Supplement D: The Chemistry of Halides and Pseudohalides (−F; −Cl; −Br; −I; $-N_3$; −OCN; −NCO etc.).

Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues.

Supplement F: The Chemistry of Amines, Nitroso and Nitro Compounds and their Derivatives.

In the present volume, as usual, the authors have been asked to write chapters in the nature of essay-reviews not necessarily giving extensive or encyclopaedic coverage of the material. Once more, not all planned chapters materialized, but we hope that additional volumes of Supplement B will appear, when these gaps can be filled together with coverage of new developments in the various fields treated.

Jerusalem, May 1979 SAUL PATAI

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C–O–C group is involved, as well as with the effects of the C–O–C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C–O–C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (*two volumes*)
The Chemistry of the Carbonyl Group (*two volumes*)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Group (*two parts*)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (*two parts*)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (*two parts*)
The Chemistry of Quinonoid Compounds (*two parts*)
The Chemistry of the Thiol Group (*two parts*)
The Chemistry of Amidines and Imidates

The Chemistry of the Hydrazo, Azo and Azoxy Groups
The Chemistry of Cyanates and their Thio Derivatives (*two parts*)
The Chemistry of Diazonium and Diazo Groups (*two parts*)
The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
Supplement A: The Chemistry of Double-bonded Functional Groups (*two parts*)
Supplement B: The Chemistry of Acid Derivatives (*two parts*)

Titles in press:

The Chemistry of Ketenes, Allenes and Related Compounds
Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues
The Chemistry of the Sulphonium Group

Future volumes planned include:

The Chemistry of Organometallic Compounds
The Chemistry of Sulphur-containing Compounds
Supplement C: The Chemistry of Triple-bonded Functional Groups
Supplement D: The Chemistry of Halides and Pseudo-halides
Supplement F: The Chemistry of Amines, Nitroso and Nitro Groups and their Derivatives

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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SAUL PATAI

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CHAPTER 1

Recent advances in the theoretical treatment of acid derivatives

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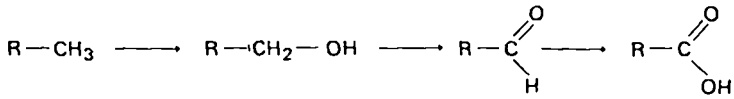
GLOSSARY OF ABBREVIATIONS

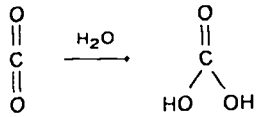
AO	atomic orbital	HF	Hartree–Fock
CI	configuration interaction	LCAO	linear combination of atomic orbitals
CMO	canonical molecular orbital		
ETF	exponential type function	LMO	localized molecular orbital
GRHF	general restricted Hartree–Fock	SCF	self-consistent field
		STO	Slater type orbital
GTF	Gaussian type function	UHF	unrestricted Hartree–Fock
GTO	Gaussian type orbital	VB	valence bond

I. INTRODUCTION

When a terminal carbon atom of a chain is oxidized to the highest level of oxidation state one obtains carboxylic acids:



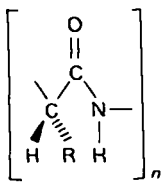
However it is not as highly oxidized as the carbon in carbon dioxide or in carbonic acid:



Carboxylic acids (**1a**) and their derivatives (**1b**) are of great importance in industry and in chemical synthesis and also play an important role in biological processes

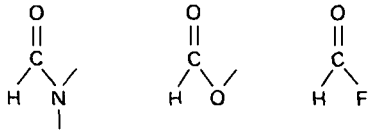
(1a) (1b)

Notably the fundamental functional group of proteins is also a carboxylic acid derivative:



Although the naturally occurring and synthetic carboxylic acids (**1a**) and their derivatives (**1b**) are in general too complicated (i.e. R involves too many electrons and too many geometrical parameters) for rigorous theoretical studies, nevertheless molecular orbital calculations have been carried out on the early members of the homologous series in which the functional groups (**1a**, **1b**) are fully present but R is only hydrogen or methyl. For this reason, in this review particular emphasis will be placed on the first members (R = H) of the homologous series although higher

members will also be discussed when appropriate. In particular, we shall place strong emphasis on the following family of compounds:



Before discussing the details of acyl derivatives it is perhaps advisable to set the limits on the compounds of the type RCOX that will qualify for the term acyl derivative. This may conveniently be done by examining the oxidation states of C in different carbon compounds as shown in Figure 1.

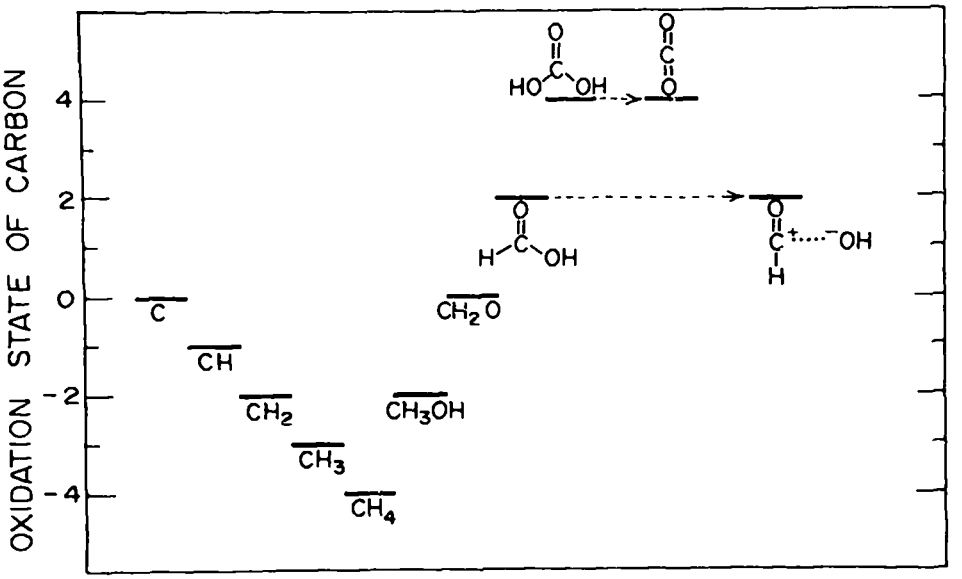
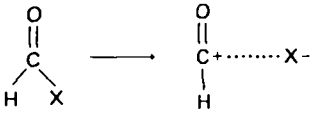
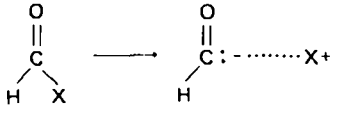


FIGURE 1. Relative oxidation states of carbon in simple compounds containing one carbon atom. Carboxylic acids and acyl derivatives contain C with a formal oxidation state of +2.

All compounds of the type HCOX where X is more electronegative than carbon (i.e. X = NH_2, OH, F etc.) lead to (at least in principle) heterolytic C—X bond cleavage of the type:



The oxidation state of carbon remains constant during dissociation. Therefore the compounds may be classified as acyl derivatives. If group X is less electronegative than carbon (i.e. X = Li, BeH, BH_2) then heterolytic dissociation of the type



is expected in which the oxidation state at carbon in $H-\overset{\overset{O}{\|}}{C}:-$ is 0 in contrast to the oxidation state at carbon in $H-C{\equiv}O^{+}$ which is +2. Thus for elements less electronegative than carbon (i.e. X = Li, BeH, BH_2, etc.) the compounds of the type HCOX or RCOX may not properly be regarded as acyl derivatives.

II. THEORY

A. Many-electron Wave Functions

For an atomic or molecular system that contains more than one electron one needs to construct a many-electron wave function (equation 1) that describes the simultaneous distribution for all the electrons in the system. The electron labels 1, 2, 3, . . . ω in equation (1) stand for the ω space and spin coordinates of the electrons. If $\omega = 1$ then one has a one-electron wave function (equation 2).

$$\Psi \equiv \Psi(1, 2, 3, \ldots \omega) \tag{1}$$

$$\Psi \equiv \Psi(1) = \begin{cases} \phi(1)\alpha(1) \\ \phi(1)\beta(1) \end{cases} \tag{2}$$

One-electron wave functions, because of their special significance, are given the name orbitals. One-electron wave functions, as shown by equation (2), may be written in spin-orbital form as a product of a space function (spatial orbital or simply orbital) ϕ and a spin function that may be either α or β. Orbitals are important on at least two accounts. First of all, they have conceptual significance, since at present most chemical interpretations are given in terms of orbitals, which may be atomic orbitals (AO), delocalized canonical molecular orbitals (CMO) or localized molecular orbitals (LMO). Their practical importance lies in the fact that many-electron wave functions are constructed from orbitals. If atomic orbitals (AO) are used to construct many-electron wave functions then the total or many-electron wave function is called a Valence Bond (VB) wave function. The many-electron wave function is synthesized in two steps. First VB structures are constructed, then a suitable linear combination of these structures yields the total many-electron VB wave function. If molecular orbitals (MO) are used as building blocks then in the first step configurations are constructed and the linear combination of these configurations yields a total many-electron wave function. This is called a configuration interaction (CI) or superposition of configurations (SOC) wave function. In either case the total wave function may be written as in equation (3), where Ψ_0 stands for the total ground-state wave function and Φ_0 may symbolize the ground or zeroth VB structure or MO configuration; Φ_1, Φ_2, ... represent the higher or excited structures or configurations and the $a_{\mu\nu}$ are the coefficients of the linear combination. Figures 2 and 3 illustrate three possible structures and configurations, respectively which one can construct for the description of the two π electrons of a carbonyl group.

$$\Psi_0(1, 2, 3, \ldots) = a_{00}\,\Phi_0(1, 2, 3, \ldots) + a_{01}\,\Phi_1(1, 2, 3, \ldots) + a_{02}\,\Phi_2(1, 2, 3, \ldots) + \ldots \tag{3}$$

Historically the use of VB-type wave functions preceded the construction of CI-type wave functions but, due to computational difficulties in the VB-type representation, the MO or MO–CI description, in one form or another, today dominates the field of molecular computation. MO are used in spite of the fact that

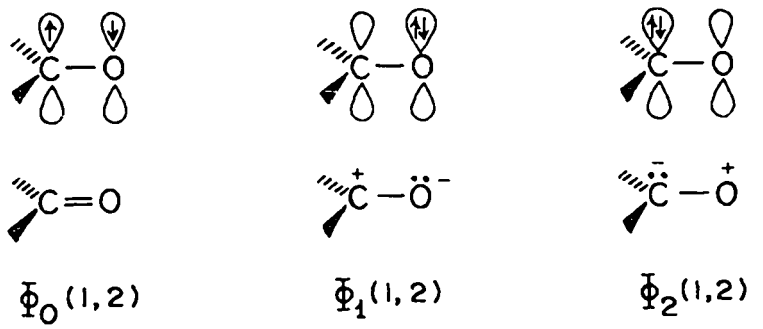


FIGURE 2. Orbital as well as dash and dot representations of three possible 'structures' used in the VB description of the π-electron distribution of a carbonyl group.

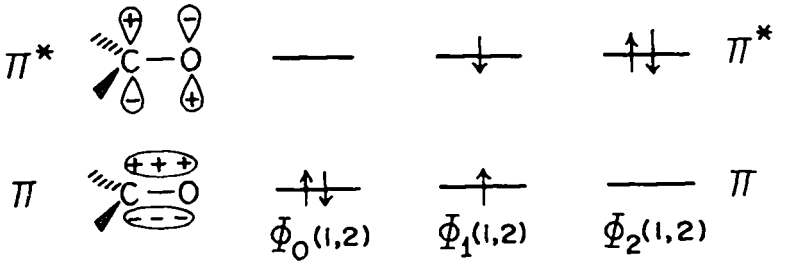


FIGURE 3. Occupancy scheme of π and π^* molecular orbitals as they occur in three possible 'configurations' used in the CI description of the π-electron distribution of a carbonyl group.

the MO (ϕ) have to be generated from the atomic orbitals (η) via another linear combination (LCAO).

$$\Phi_i = \sum_{j=1}^{N} \eta_j C_{ji} \tag{4}$$

The fundamental reason why the MO representation is favoured is due to the fact that a wave function in which only the leading Φ_0 term is retained in equation (3) and all others are neglected (i.e. an expansion which is infinite, at least in principle, is truncated after the first term), is still able to yield about 99.5% of the total molecular energy. When only the ground configuration Φ_0 is retained, a_{00}, the weighting coefficient, becomes unity due to normalization. For an even number ($2M$) of electrons, this ground configuration is frequently written as a $2M \times 2M$ Slater determinant, which in turn is constructed from M one-electron spatial functions $\{\phi\}$ (i.e. MO) and two one-electron spin functions α and β:

$$\Psi(1, 2, 3, \ldots 2M) \approx \Phi_0(1, 2, 3, \ldots 2M) = \frac{1}{\sqrt{(2M)!}} \begin{vmatrix} \phi_1(1)\alpha(1) & \phi_1(1)\beta(1) \ldots & \phi_M(1)\beta(1) \\ \phi_1(2)\alpha(2) & \phi_1(2)\beta(2) \ldots & \phi_M(2)\beta(2). \\ \vdots & \vdots & \vdots \\ \phi_1(2M)\alpha(2M) & \phi_1(2M)\beta(2M) \ldots & \phi_M(2M)\beta(2M) \end{vmatrix} \tag{5}$$

B. The Variation Theorem

The total ground-state electronic energy is computed from the above wave function as the expectation value of the molecular electronic Hamiltonian $\hat{H}_e$:

$$E_0(1, 2, 3, \ldots 2M) =$$

$$\langle \Phi_0(1, 2, 3, \ldots 2M) | \hat{H}_e(1, 2, 3, \ldots 2M) | \Phi_0(1, 2, 3, \ldots 2M) \rangle \tag{6}$$

The MO ϕ are generated from the N AO η as defined by equation (4) or as shown in detail in equation (7). The total ground-state electronic energy may only be calculated from equation (6) if the coefficient matrix **C** of equation (7) is known. Since initially **C** is unknown one normally resorts to the variation theorem that states that the best Φ_0 yields the lowest energy E_0. Consequently the minimization of E_0 with respect to the building blocks from which Φ_0 is constructed should yield the best Φ_0 since Φ_0 is constructed from a set of variable $\{\phi\}$, i.e. MO, which are in turn obtained from a set of fixed $\{\eta\}$, i.e. AO, and a variable coefficient matrix. The minimization of E_0 can be done in terms of **C** after equation (7) is substituted into equation (5) which is in turn substituted into equation (6).

$$(\phi_1\ \phi_2 \ldots\ldots \phi_N) = (\eta_1\ \eta_2 \ldots\ \eta_N) \begin{pmatrix} C_{11}\ C_{12} \ldots\ldots\ldots C_{1N} \\ C_{21}\ C_{22} \ldots\ldots\ldots C_{2N} \\ \vdots \\ C_{N1}\ C_{N2} \ldots\ldots\ldots C_{NN} \end{pmatrix} \tag{7a}$$

or in brief:

$$\phi = \eta \mathbf{C} \tag{7b}$$

This optimization leads to a set of linear equations commonly known as the Hartree–Fock equations that can be solved iteratively for **C**. The solution also yields a set of MO energies (ϵ_i), of which the lowest M will be occupied and the highest $(N - M)$ will be unoccupied.

This single determinantal wave function (equation 5) clearly will not yield as low an energy as the complete expansion equation (3), and the lowest energy that could be attained by the Hartree–Fock method is termed the Hartree–Fock Limit (HFL). The additional configurations in the CI expansion (equation 3) account for the effects the electron pairs have on one another, since they tend to correlate their motions to reduce electron–electron repulsion. As the expansion becomes more complete (that is, more terms are included) the CI wave function gives an energy which approaches another limiting value, the Non-Relativistic Limit (NRL). The energy difference between the HFL and the NRL is called the correlation energy, and it increases as the number of electron pairs becomes larger.

To obtain the experimental energy, the molecular Hamiltonian (see Section II.C) must be changed to include relativistic effects. The relativistic energy is zero for hydrogen and small for light elements (Li → F), but increases with atomic number. Relativistic effects are most important for inner-shell electrons and thus are not often of chemical importance.

C. Closed-shell Hartree–Fock Problems

The main points of the Hartree–Fock procedure[1] carried out within the Born–

Oppenheimer (fixed nuclei) approximation may be summarized as follows:

(*i*) The wave function which describes the electronic ground state of a $2M$ electron system has the form of a $2M \times 2M$ determinant as seen in equation (5).

$$\hat{H} \equiv \hat{H}(1, 2, \ldots 2M) = \sum_{u=1}^{2M} \hat{h}_u + \frac{1}{2} \sum_{u=1}^{2M} \sum_{\substack{v=1 \\ v \neq u}}^{2M} \hat{g}_{uv} \tag{8}$$

(*ii*) The electronic Hamiltonian for the $2M$ electron system may be written as in equation (8) where $\hat{h}$ is the nuclear–electron attraction operator plus the electron kinetic energy operator, and $\hat{g}$ is the electron–electron repulsion operator.

(*iii*) The electronic energy, after substitution of Φ_0 and $\hat{H}$ into equation (6) is:

$$E^e = \langle \Phi_0 \mid \hat{H} \mid \Phi_0 \rangle \tag{9}$$

The total energy may be calculated by adding the nuclear repulsion energy. Integrating out the spin variables, this energy expression becomes:

$$E^e = 2 \sum_{p=1}^{M} \langle \phi_p(1) \mid \hat{h}_1 \mid \phi_p(1) \rangle + \sum_{p=1}^{M} \sum_{q=1}^{M} [2 \langle \phi_p(1)\phi_q(2) \mid \hat{g}_{12} \mid \phi_p(1)\phi_q(2) \rangle - \langle \phi_p(1)\phi_p(2) \mid \hat{g}_{12} \mid \phi_q(1)\phi_q(2) \rangle] \tag{10}$$

where the two electron integrals (the last two terms in equation 10) are the coulomb and exchange integrals. Note that in the columb integrals, electron 1 is associated with orbital ϕ_p and electron 2 is associated with orbital ϕ_q. This distinction between coulomb and exchange terms becomes clearer in the electron density formalism where orbitals associated with electron 1 are collected in front of the operator while those associated with particle 2 are written behind the operator:

$$E^e = 2 \sum_{p=1}^{M} \langle \phi_p(1) \mid \hat{h}_1 \mid \phi_p(1) \rangle + \sum_{p=1}^{M} \sum_{q=1}^{M} [2\{\phi_p(1)\phi_p(1) \mid \phi_q(2)\phi_q(2)\} - \{\phi_p(1)\phi_q(1) \mid \phi_p(2)\phi_q(2)\}] \tag{11}$$

Note that in order to dintinguish the electron density formalism (equation 11) from the traditional notation (equation 10) the brackets are changed from $\langle \mid \mid \rangle$ to $\{ \mid \}$ and the electron–electron repulsion operator $\hat{g}_{uv}$ is omitted but is implicitly understood to be present.

According to the Variation Theorem the energy may be optimized by variation of ϕ_p. The expansion of the $2M$ ϕ in terms of the known set of N AO (equation 7) which may be written in matrix notation as:

$$\phi = \eta \mathbf{C} \tag{12}$$

or

$$\phi^\dagger = C^\dagger \eta^\dagger \tag{13}$$

results in the Hartree–Fock matrix equation over the AO basis:

$$C^\dagger F^\eta C = C^\dagger S^\eta C \epsilon \tag{14}$$

where

$$F^\eta = h^\eta + 2J^\eta - K^\eta \tag{15}$$

$$S_{ij}^{\eta} = \langle \eta_i \mid \eta_j \rangle \tag{16}$$

ϵ is a diagonal matrix ($\epsilon_{pq} = 0$ for $p \neq q$) of elements ϵ_{pp}, which are the orbital energies associated with MOs, and S is the atomic orbital overlap matrix. The molecular integrals involved in equation (15) have the usual one-electron or pseudo one-electron form:

$$h_{ij}^{\eta}(1) = \langle \eta_i(1) \mid \hat{h} \mid \eta_j(1) \rangle \tag{17}$$

$$J_{ij}^{\eta}(1) = \sum_{k=1}^{N} \sum_{l=1}^{N} \{\eta_i(1)\eta_j(1) \mid \eta_k(2)\eta_l(2)\}\rho_{kl} \tag{18}$$

$$K_{ij}^{\eta}(1) = \sum_{k=1}^{N} \sum_{l=1}^{N} \{\eta_i(1)\eta_k(1) \mid \eta_j(2)\eta_l(2)\}\rho_{kl} \tag{19}$$

$$\rho = \begin{pmatrix} C_{11} & C_{12} & \dots & C_{1M} \\ C_{21} & C_{22} & \dots & C_{2M} \\ \vdots & \vdots & & \vdots \\ C_{N1} & C_{N2} & \dots & C_{NM} \end{pmatrix} \begin{pmatrix} C_{11} & C_{21} & \dots & C_{N1} \\ C_{12} & C_{22} & \dots & C_{N2} \\ \vdots & \vdots & & \vdots \\ C_{1M} & C_{2M} & \dots & C_{NM} \end{pmatrix} \tag{20a}$$

$$\rho = \mathbf{C}\mathbf{C}^{+} \tag{20b}$$

Thus the Fock matrix can be written

$$F_{ij} = \langle \eta_i \mid \hat{h} \mid \eta_j \rangle + \sum_{k}^{N} \sum_{l}^{N} [2\{\eta_i\eta_j \mid \eta_k\eta_l\} - \{\eta_i\eta_k \mid \eta_j\eta_l\}]\rho_{kl} \tag{21}$$

In terms of the AO, E^{e} can be written as

$$E^{e} = 2\sum_{i}^{N}\sum_{j}^{N} \rho_{ij}\hat{h}_{ji} + 2\sum_{i}^{N}\sum_{i}^{N} \rho_{ij}J_{ji} - \sum_{i}^{N}\sum_{j}^{N} \rho_{ij}K_{ji} \tag{22}$$

The solution of the Hartree–Fock equation (14) for the coefficient matrix C and for the molecular orbital energy matrix ϵ involves the following computational procedure.

Two matrices, the overlap matrix (S) and the Fock matrix (F) are required. The elements of the S matrix may be computed directly but the elements of the F matrix, F_{ij}, are assembled according to equation (21). It is clear however that the F_{ij} depend on the density matrix ρ which, in turn, is computed from the coefficient matrix C according to equation (20). Thus the final F matrix cannot be assembled until the Hartree–Fock problem is solved, but the problem cannot be solved until the F matrix is set up.

This paradox leads to an iterative process where C is initially assumed and F is calculated in terms of this arbitrary C. When the approximate Fock matrix is assembled, the Hartree–Fock equation is solved, yielding a new C matrix and the problem may be solved for the second time starting with the new F

This iterative process is called the Self-Consistent Field (SCF) method. In the course of the SCF procedure the total energy (E^{e}) is lowered in each iterative cycle and the convergence to any desired accuracy is measured by the difference between the energy values associated with two successive iterations ($E_n^{e} = E_{n-1}^{e} - E_n^{e}$). The overall SCF process is illustrated in Figure 4.

The most fundamental decision involved in these calculations is the choice of the types of basis function η. Two types of functions are widely used, depending on the

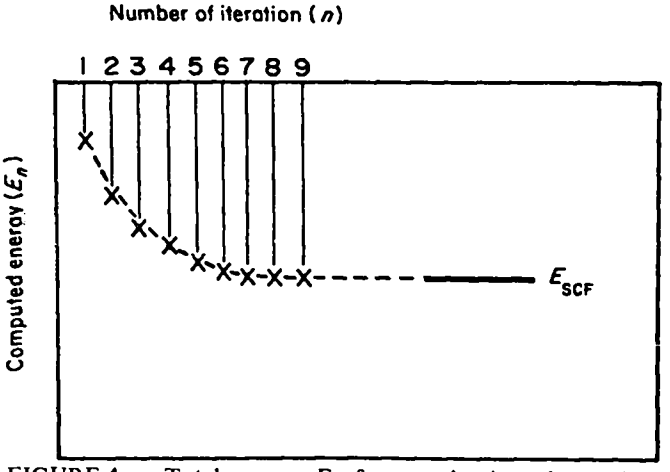


FIGURE 4. Total energy E of successive iterations using the SCF method.

size of the system. One is Exponential-Type Functions (ETF), frequently called Slater-Type Orbitals (STO), the other is Gaussian-Type Functions (GTF), sometimes referred to as Gaussian-Type Orbitals (GTO). The most important difference between these two types of η is that in the former one the function decays exponentially (to the first power of r) while in the latter the decay takes place to r^2.

$$\text{ETF(STO)} \quad \eta_E = N_E r^{(n-1)} e^{-\xi r} Y_{l,m}(\theta, \phi) \tag{23a}$$

$$\text{GTF(GTO)} \quad \eta_G = N_G r^{(n-1)} e^{-\xi r^2} Y_{l,M}(\theta, \phi) \tag{23b}$$

Figure 5 shows 1s-type functions for ETF and GTF. The three different s-GTF shown (heavy lines) have numerically different orbital exponents (ξ). On the whole, ETF are more accurate and are widely used for small systems. For larger molecules, computational difficulties arise and GTF are more practical.

However, for complex systems such as HCOOH the size of the GTF basis set becomes unmanageable since three times as many GTF as ETF are necessary to obtain results of comparable accuracy. For this reason, these primitive GTF are contracted to approximate ETF and this contracted AO basis set, which is very much reduced in size, is used for the SCF calculation.

The traditional basis sets are the minimal (or single-zeta) basis and the double-zeta basis. These are specified in the following way:

Minimal basis

H	$1s$	
C, N, O, F	$1s, 2s, 2p_x, 2p_y, 2p_z$	(24)
Si, P, S, Cl	$1s, 2s, 2p_x, 2p_y, 2p_z, 3s, 3p_x, 3p_y, 3p_z$	

Double-zeta basis

H	$1s, 1s'$	
C, N, O, F	$1s, 1s', 2s, 2s', 2p, 2p'$	(25)
Si, P, S, Cl	$1s, 1s', 2s, 2s', 2p, 2p', 3s, 3s', 3p, 3p'$	

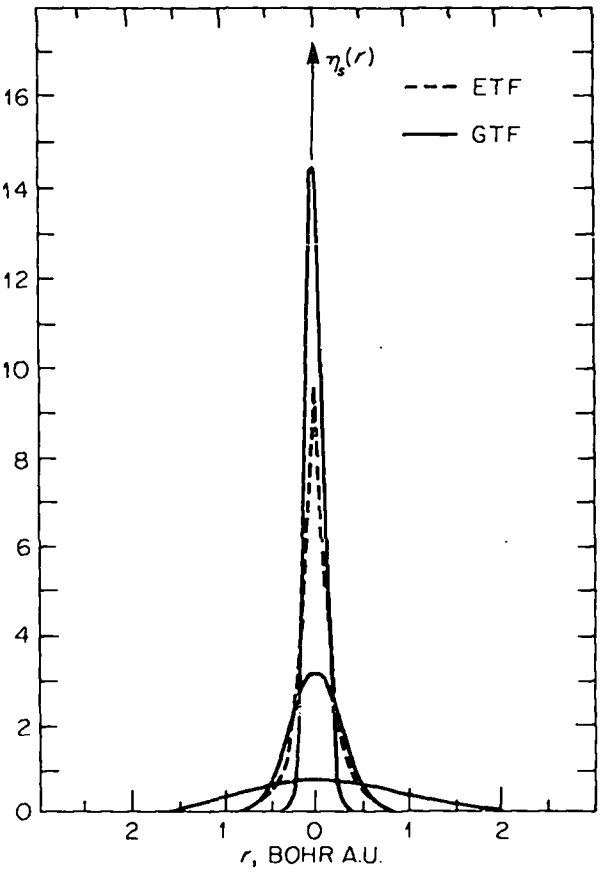


FIGURE 5. Exponential-type function (ETF) and Gaussian-type functions (GTF) for a 1s orbital.

In the latter notation $2p$ and $3p$ stand collectively for $2p_x$, $2p_y$, $2p_z$, and $3p_x$, $3p_y$, $3p_z$. The term 'double-zeta' originates from the fact that the primed and unprimed orbitals such as $1s$, $1s'$ differ only in their orbital exponents ξ and ξ'.

When primitive GTF are contracted they usually form either the minimal basis set or the double-zeta basis set. It should be emphasized that a double-zeta basis set is often mandatory to obtain significant results, and more extensive than double-zeta basis sets are not uncommon.

D. Open-shell Hartree–Fock Problems

The conceptual and computational problems in restricted open-shell SCF theory arise because, in general, the wave function is an expansion involving more than one determinant:

$$\Psi = b_1\Phi_1 + b_2\Phi_2 + \ldots \tag{26}$$

where the Φ_i are Slater determinants which have all possible distributions of the unpaired electron amongst the orbitals of the partly filled shells. The coefficients b_i

are determined by group theoretical considerations. As a consequence the Fock operator has a complicated structure which depends upon the b_i.

The form of the Fock operator is given most succinctly in the basis of the 'trial' MO. If we use subscripts R, S for doubly occupied MO, U, V, X, Y for 'valence' or 'open-shell' MO, A, B, C, D for virtual orbitals and finally I, J, K, L for arbitary MO we can define the operators

$$\langle \phi_I \mid \hat{F}_1 \mid \phi_K \rangle = 2 \langle \phi_I \mid \hat{h}^c + \sum_{U>V} (\hat{J}^{\phi}_{UV} - \hat{K}^{\phi}_{UV}) \gamma_{UV} \mid \phi_K \rangle \tag{27}$$

$$\langle \Phi_I \mid \hat{F}_2 \mid \phi_J \rangle = \langle \phi_I \mid \left\{ \sum_Z \hat{h}^c \mid \phi_Z \rangle \gamma_{ZJ} + \sum_{U>V} \hat{J}^{\phi}_{UV} \mid \Phi > \Gamma_{JZUV} - \hat{K}_{UV} \mid \phi_Z \rangle \Gamma_{JUZV} \right\} \tag{28}$$

with

$$\hat{h}^c = \hat{h} + \sum_A (2\hat{J}_A - \hat{K}_A) \tag{29}$$

$$\hat{J}^{\phi}_{UV} = \int \frac{\phi_U(1)\,\phi_V(1)}{r_{12}}\, dr_1 \tag{30}$$

$$\hat{K}^{\phi}_{UV} = \int \frac{\phi_U(1)\,\phi_V(1)}{r_{12}}\, P_{12} \tag{31}$$

The density matrices γ_{IJ} and Γ_{IJKL} are determined from group theoretical considerations and involve the b_i from equation (26). The final Fock operator is given in matrix form as:

	$\{\phi_R\}$	$\{\phi_U\}$	$\{\phi_A\}$
$\{\phi_R\}$	NUD	$F_1 - F_2$	F_1
$\{\phi_U\}$	$F_1 - F_2$	NUD	F_2
$\{\phi_A\}$	F_1	F_2	NUD

(32)

The diagonal blocks are not uniquely defined (NUD) and one may use any linear combination of F_1 and F_2. As a consequence the orbitals and orbital energies do not have any simple significance as in the closed-shell problem. However, while the formulae for the Fock operator may seem rather formidable, the calculations are only slightly more difficult to perform than the closed-shell case.

The general expression for the total energy in the open-shell case is also rather complicated:

$$E = E_c + \sum_{I,J} \left[\sum_{U,V} \gamma^{IJ}_{UV} \langle U \mid \hat{h} \mid V \rangle b_I b_J + \sum_{U,V,X,Y} \langle UV \mid XY \rangle \Gamma^{IJ}_{UVXY} b_I b_J \right] \tag{33}$$

with

$$E_c = \sum_A 2\, h^{\phi}_{AA} + \sum_{AB} G^{\phi}_{AB} \tag{34}$$

where the density matrices γ^{IJ}_{UV} and Γ^{IJ}_{UVZY} are again computable from group theoretical considerations. One observes that the 'closed-shell' part of the energy E_c is the same as that observed previously (equation 22).

A simple example may serve to clarify the above discussion. Consider the three singlet states that can arise from a situation where one has two electrons in a pair of

degenerate orbitals ϕ_U and ϕ_V:

$$\Psi_{I,II} = 2^{-1/2}\{ |\underbrace{\phi_U(1)\bar{\phi}_U(2)}_{\Phi_1}| \pm |\underbrace{\phi_V(1)\bar{\phi}_V(2)}_{\Phi_2}| \} \tag{35}$$

$$\Psi_{III} = 2^{-1/2} \underbrace{\{ |\phi_U(1)\bar{\phi}_V(2)| - |\bar{\phi}_U(1)\phi_V(2)| \}}_{\Phi_3} \tag{36}$$

If U and V were of π symmetry in point group $C_{\infty v}$ then Φ_1 has Σ^+ symmetry, Φ_2 and Φ_3 have Δ symmetry. Some of the symbolic density matrices are tabulated below. For γ_{UU} we obtain:

$$\begin{array}{c} \\ \Phi_1 \\ \Phi_2 \\ \Phi_3 \end{array} \begin{array}{c} \begin{array}{ccc} \Phi_1 & \Phi_2 & \Phi_3 \end{array} \\ \begin{pmatrix} 2 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \end{array}$$

while γ_{UV} has the following explicit form:

$$\begin{array}{c} \\ \Phi_1 \\ \Phi_2 \\ \Phi_3 \end{array} \begin{array}{c} \begin{array}{ccc} \Phi_1 & \Phi_2 & \Phi_3 \end{array} \\ \begin{pmatrix} 0 & 0 & \sqrt{2} \\ 0 & 0 & \sqrt{2} \\ \sqrt{2} & \sqrt{2} & 0 \end{pmatrix} \end{array}$$

and finally Γ_{UVUV} has the following form:

$$\begin{array}{c} \\ \Phi_1 \\ \Phi_2 \\ \Phi_3 \end{array} \begin{array}{c} \begin{array}{ccc} \Phi_1 & \Phi_2 & \Phi_3 \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix} \end{array}$$

The coefficients of Φ_1, Φ_2 and Φ_3 in the expansion of Ψ_I, Ψ_{II} and Ψ_{III} are just the Clebsch–Gordon coefficients for two spin angular moments ($s = \frac{1}{2}$). The numbers in the symbolic density matrices are most easily obtainable from group theoretical methods[2].

The above methods are a form of General Restricted Hartree–Fock (GRHF) theory. In the special case where one has (*a*) no degenerate orbitals and (*b*) all the unpaired electrons have the same spin, it is possible to simplify the above formulation considerably. In this case it is possible to set up two independent HF equations (Spin-Unrestricted Hartree–Fock SUHF), one for α spin and one for β spin. These equations are almost identical to those for the closed shell and there is little point in discussing the details. It is important to point out that in this technique the wave function no longer corresponds to a correct spectroscopic state and GRHF will give a lower energy.

Finally, it should be pointed out in the early applications of GRHF one encountered severe numerical instabilities in actually solving the equation. The SUHF equations were often used simply because these difficulties could be avoided. However, at present, it is possible to handle almost any open-shell situation within GRHF.

E. Correlation of Theoretical Results with Experimental Observations

One of the postulates of quantum mechanics is that there exists a 1:1 correspondence between the measured value of an observable (Ω_{exp}) and the computed quantum-mechanical value (Ω_{calc}) provided the exact molecular wave function is known. Some observables are defined, in terms of quantum mechanics, as expectation values of operators. For example, for operator $\hat{\Omega}$ the expectation value Ω, that is the observable, is computed from the molecular wave function Φ as follows:

$$\Omega_{calc} = \langle \Phi \mid \hat{\Omega} \mid \Phi \rangle \tag{37}$$

The operator $\hat{\Omega}$ may be written as a sum of operators (equation 38) where $\hat{\Omega}_0$ acts on the nuclear (no-electron) wave function, $\hat{\Omega}_1$ is the one-electron contribution, as this portion of $\hat{\Omega}$ depends on the coordinates of only one electron, and $\hat{\Omega}_2$ is the two-electron operator, which depends on the coordinates of two electrons simultaneously.

$$\hat{\Omega} = \hat{\Omega}_0 + \hat{\Omega}_1 + \hat{\Omega}_2 \tag{38}$$

All observables which are defined as in equation (37) are called primary properties, and may be calculated from the various contributions given in equation (38), using the molecular wave function.

Some molecular properties such as the dipole moment (μ) and other moments correspond to one-electron operators and may be readily computed as in equation (37),

$$\mu_{calc} = \langle \Phi \mid \hat{\mu} \mid \Phi \rangle \tag{39}$$

and may be compared with the experimentally measured value (μ_{exp}).

Of course, for a perfect correlation (that is for a 1:1 correspondence) we should have the exact molecular wave function, which we never know. Consequently the comparison we make between μ_{exp} and μ_{calc} may be taken as a test of the accuracy of the wave function. Unfortunately μ_{calc} does not converge monotonically to μ_{exp}. This non-monotonic behaviour is illustrated in Figure 6 for formamide (see also Table 11).

Only in the limiting case (at the Hartree–Fock Limit) will the two values be numerically close enough. For a carboxylic acid or for its derivatives the situation is much more complicated than it is for a diatomic molecule. For a polyatomic molecule not only the magnitude of the dipole moment but its direction may also change with increased basis set size. This pattern is illustrated for formamide in Figure 7, using data from Table 2.

The situation is far more complicated in the case of energy calculations. The source of the complication is twofold.

First of all the energy cannot be computed as accurately as some other properties such as dipole moment. The operator needed to calculate the energy (E) (equation 40), the Hamiltonian operator ($\hat{H}$), is a two-electron operator (it includes terms that simultaneously depend on the coordinates of two electrons which involve many two-electron integrals of the form of equation 18) while the dipole moment operator is a one-electron operator (only up to a single electron coordinates are used explicitly).

$$E = \langle \Phi \mid \hat{H} \mid \Phi \rangle \tag{40}$$

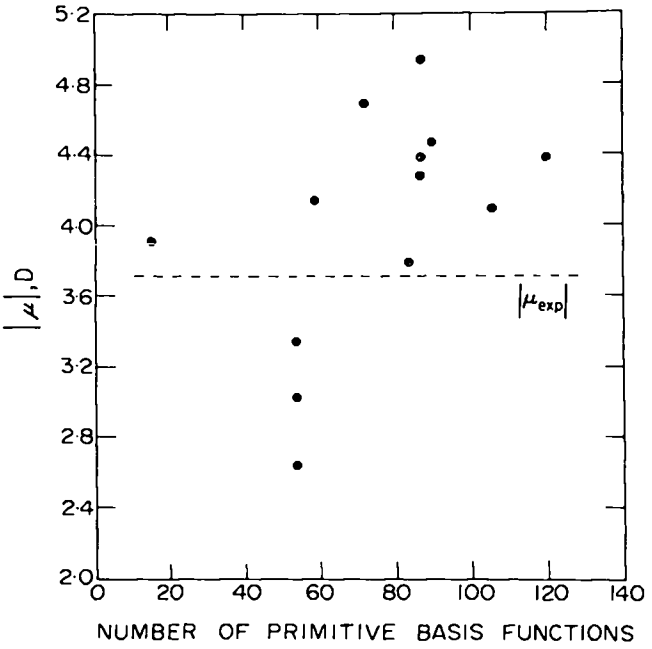


FIGURE 6. Non-monotonic behaviour of the magnitude of the dipole moment of $HCONH_2$ with basis-set size.

Secondly, total energy as computed by the above equation cannot be observed. We may observe energy differences only. For example the total energy of a carbon atom (E_C) may be computed from the wave function of the carbon atom (Φ_C) and the Hamiltonian of the carbon atom ($\hat{H}_C$) but experimentally we can determine only ionization potentials. The experimental E_C is taken to be the sum of the six ionization potentials (I_i) of C

$$\langle \Phi_C \mid \hat{H}_C \mid \Phi_C \rangle = E_C = \sum_{i=1}^{6} I_i \tag{41}$$

where each ionization potential is a difference of two energy values associated with two states of ionization (n.b. the bare nucleus has zero energy by definition, i.e. $E_{C^{++++++}} = 0$):

$$\begin{aligned} I_1 &= E_{C^+} - E_C \\ I_2 &= E_{C^{++}} - E_{C^+} \\ I_3 &= E_{C^{+++}} - E_{C^{++}} \\ I_4 &= E_{C^{++++}} - E_{C^{+++}} \\ I_5 &= E_{C^{+++++}} - E_{C^{++++}} \\ I_6 &= E_{C^{++++++}} - E_{C^{+++++}} \end{aligned} \tag{42}$$

In all processes we are primarily interested in energy differences since the experimentally determined value represents an energy difference. For example, the rotation about the C—OH bond in formic acid is characterized by two energy differences, a kinetic and a thermodynamic value as shown by Figure 8.

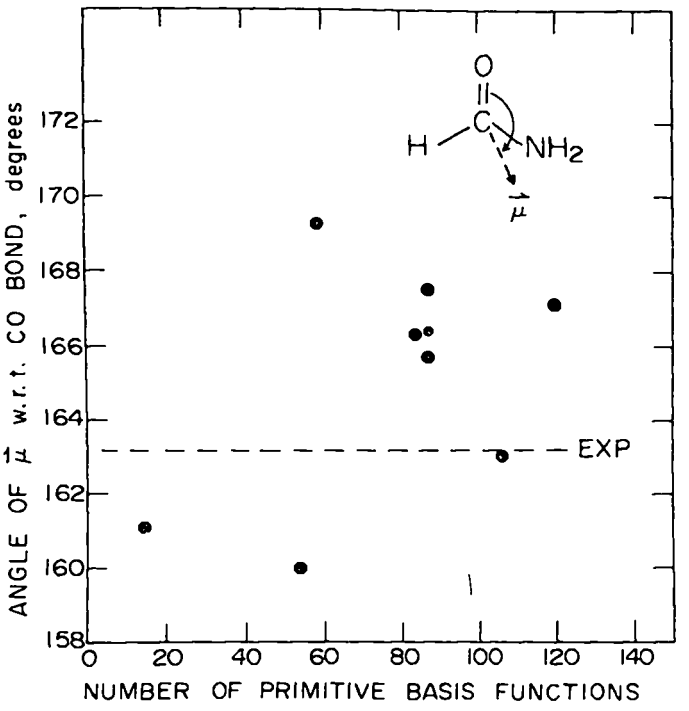
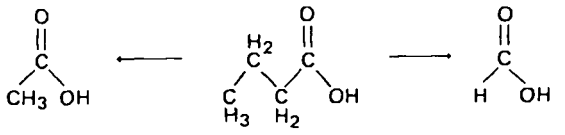


FIGURE 7. Variation in the direction of the formamide dipole moment with basis-set size. The dipole moment is measured clockwise with respect to the CO bond.

If we could be sure that the theoretically determined curve is parallel to the experimental one we could declare that as far as energy differences are concerned we have perfect agreement with experiment even if the total energies differ. As may be seen from this figure there may be some differences but the two patterns, qualitatively or even semiquantitatively, may be the same. We could conclude with some confidence that as long as we are investigating processes (like the C—OH rotation discussed above) in which the electron pairing scheme is preserved we may compute reliable energy differences provided we use at least a moderately extensive basis set. In other words, for processes which do not change the number of electron pairs, we expect that the experimental behaviour is reproduced at the SCF level since the correlation energy change will be small (note that the relativistic energy is unchanged to a high degree of approximation for most reactions).

Another major problem we must face is the size of a molecule. For example a carboxylic acid is usually too large for rigorous calculations, consequently we frequently wish to model the behaviour of a larger acid by a smaller one. If the process under investigation occurs in the carboxylic functional group, a larger acid, say butyric acid, may be mimicked by formic acid:



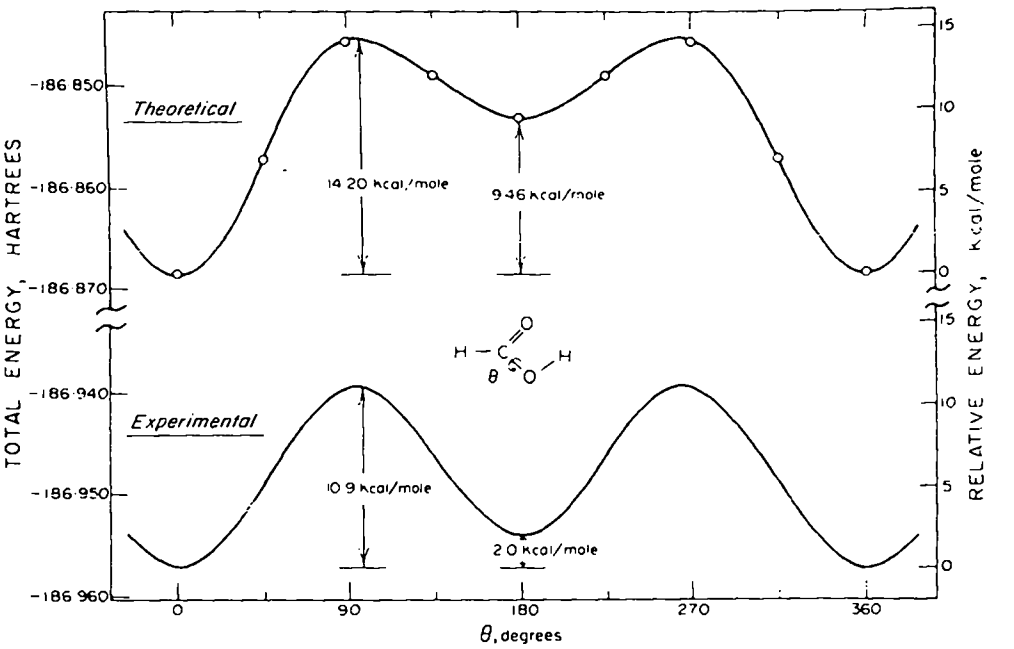


FIGURE 8. Theoretical and experimental potential curves for hydroxyl rotation in formic acid. The kinetic energy differences are the barrier heights, and the thermodynamic differences are the relative energies of the $\theta = 0°$ and $\theta = 180°$ conformers. Reproduced with permission from A. C. Hopkinson, K. Yates and I. G. Csizmadia, *J. Chem. Phys.*, **52**, 1784 (1970).

If on the other hand the phenomenon is associated with the α-carbon atom we may use acetic acid as an analogue of butyric acid.

Accumulated experience shows that studying model problems instead of the actual problem may lead to a great deal of understanding of the problem at hand.

The determination of molecular geometry such as the C=O bond length in a carboxylic acid is further complicated by the fact this is not a primary but a derivative property. In other words one must take the derivative of the expectation value of the Hamiltonian in a minimization process and solve the equation (43) for r_{CO}.

$$\frac{\partial E}{\partial r_{CO}} = \frac{\partial \langle \Phi | \hat{H} | \Phi \rangle}{\partial r_{CO}} = 0 \tag{43}$$

The first derivative of the energy with respect to some coordinate (e.g. the bond length or bond angle) is the force along that coordinate[3]. The second derivative for example equation (44), is the associated force constant. These force constants may be used to obtain vibrational frequencies through Wilson's GF matrix method[4,5].

$$\frac{\partial^2 E}{\partial r_{CO}^2} \tag{44}$$

The optimum r_{CO} obtained by this theoretical calculation usually differs slightly from the experimental value but as a general rule even a moderately extensive calculation gives bond lengths within say 0.05 Å.

III. PHYSICAL PROPERTIES

A. General Theoretical Considerations

For the description of any particle one needs three coordinates (x, y, z) and consequently for an N-atom molecule one needs $3N$ coordinates. Instead of specifying the three coordinates of each N atoms it is customary to divide the $3N$ coordinates into translational, rotational and vibrational modes. Out of the $3N$ coordinates three coordinates are reserved to specify the centre of mass of the molecule (three translational modes), three coordinates are reserved to describe the rotation of the molecule around its three principal axes of inertia (three rotational modes) and the remaining $3N - 6$ coordinates describe the internal motion of the atoms (vibrational modes). Since normally one investigates a stationary molecule, it is necessary to allow for the variation of the $3N - 6$ internal modes only. All of this leads to the fact that the molecular energy is a function of $3N - 6$ independent internal coordinates:

$$E = E(q_1, q_2, q_3 \ldots, q_{3N-6}) \tag{45}$$

This multi-dimensional function E is normally referred to as an energy hypersurface and it describes the energetics of all possible nuclear arrangements of the N atoms. Consequently stable structures, including all possible isomers and tautomers, represent the minima of this multi-dimensional function E and saddle points of this function E may be associated with the transition states of tautomerizations, molecular rearrangements as well as conformational changes. In that sense the analysis of the energy hypersurface is necessary for the understanding of the molecular geometries and stereochemistry.

The points on the hypersurface that are of interest, namely the minima, saddle points and maxima, are critical points where the gradient of E (the force – see equation 43) with respect to each and every internal coordinate is zero:

$$\left(\frac{\partial E}{\partial q_1}, \frac{\partial E}{\partial q_2}, \ldots \frac{\partial E}{\partial q_{3N-6}}\right) = (0,0, \ldots 0) \tag{46}$$

They may be distinguished by their Hessian matrix H (the force constant matrix – see equation 44), which is defined as follows:

$$\mathbf{H} = \begin{bmatrix} \dfrac{\partial^2 E}{\partial q_1^2} & \dfrac{\partial^2 E}{\partial q_1 \partial q_2} & \cdots & \dfrac{\partial^2 E}{\partial q_1 \partial q_{3N-6}} \\ \dfrac{\partial^2 E}{\partial q_2 \partial q_1} & \dfrac{\partial^2 E}{\partial q_2^2} & \cdots & \dfrac{\partial^2 E}{\partial q_2 \partial q_{3N-6}} \\ \vdots & \vdots & & \vdots \\ \dfrac{\partial^2 E}{\partial q_{3N-6} \partial q_1} & \dfrac{\partial^2 E}{\partial q_{3N-6} \partial q_2} & \cdots & \dfrac{\partial^2 E}{\partial q_{3N-6}^2} \end{bmatrix} \tag{47}$$

At a minimum, all the eigenvalues of **H** are positive, or in other words, all the second derivatives of the energy ('force constants') of the Normal Coordinates Q_i

are positive:

$$\frac{\partial^2 E}{\partial Q_i^2} > 0 \quad \text{for all } i \tag{48}$$

At a maximum, all the eigenvalues are negative:

$$\frac{\partial^2 E}{\partial Q_i^2} < 0 \quad \text{for all } i \tag{49}$$

Saddle points have indefinite Hessian matrices – that is, some eigenvalues are positive and others are negative. The number of negative eigenvalues is called the order of the critical point.

Thus minima are zero-order critical points and maxima are $3N - 6$-order critical points. The lowest energy saddle point between two minima is a critical point of order 1 since there is only one coordinate along which the energy is a maximum, being a minimum along the other $3N - 7$ coordinates. This minimum-energy pathway is called the reaction coordinate. Other saddle points of the same or higher order with higher energy may lie between two minima.

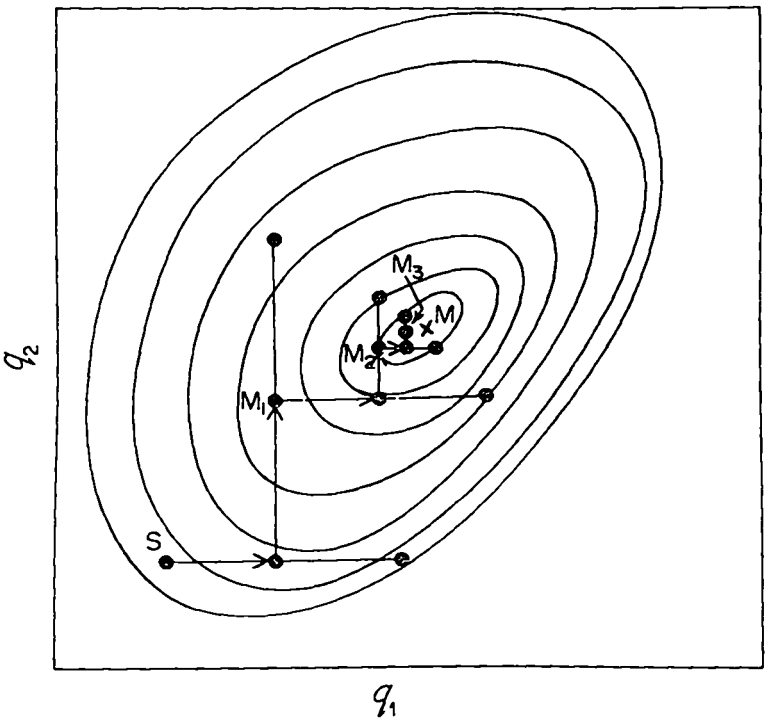


FIGURE 9. Cyclic optimization with two internal coordinates, q_1 and q_2. The contours represent $E(q_1, q_2)$, and the true minimum is marked M. The optimization starts at S, and would reach M_1 after one cycle through each coordinate, M_2 after two cycles, M_3 after three cycles, etc. The points shown indicate the three points used per coordinate per cycle to generate an interpolating parabola to predict the minimum for that coordinate.

The search for the optimal geometries by theoretical methods is by no means a trivial task. For one thing the energy hypersurface (equation 45) obtained by *ab initio* MO calculations is basis-set dependent; this means that two hypersurfaces generated by two different basis sets need not have their absolute (or relative) minima at identical molecular geometries. More often than not, the energy hypersurface is not given and the optimization procedure which is used in the search for the absolute (or relative) minimum calculates only a limited number of points on the unknown hypersurface.

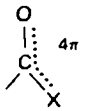
The procedure is particularly severe when only one internal coordinate (bond length, bond angle, etc.) is varied at a time. In this particular case the minimum may only be reached by an infinite number of cycles through all the internal coordinates and therefore in a finite number of cycles one can hope to approximate the minimum within a reasonable degree of accuracy (see Figure 9).

It should perhaps be emphasized that more often than not this procedure is used in obtaining the optimized geometries, as it is much simpler than explicitly solving the force equations[3]

$$\frac{\partial E}{\partial q_i} = 0 \tag{50}$$

for all internal coordinates q_i, using analytical (or numerical) derivatives of the energy.

When a heteroatom is attached to a carbonyl group, the heteroatom contributes a lone pair to the π-electron system. Consequently acid derivatives may be regarded as a four π-electron three-atom system:



This extended π system has an extra stabilization which is manifested in the shortening of the C—X bond length. The optimum C—X bond lengths obtained for selected methyl and formyl derivatives are summarized in Table 1 and illustrated in

TABLE 1. A comparison of theoretical and experimental C–X bond lengths for some CH_3–X and HCO–X compounds

	Me–X			HCO–X		
X	STO-3G[a]	4-31G[b]	Exp[c]	STO-3G[d]	4-31G[b]	Exp[e]
F	1.384	1.411[f]	1.385	1.351	1.345	1.342
OH	1.433	1.440[g]	1.428	1.382	1.348	1.329
NH_2	1.486	1.440	1.474	1.404	–	1.360

[a] Optimized bond lengths from Reference 6.
[b] This work.
[c] Averages of experimental values, Reference 7.
[d] Reference 8.
[e] Averages of experimental determinations, see Sections III.B, III.C and III.D.
[f] See also Reference 9.
[g] See also Reference 10.

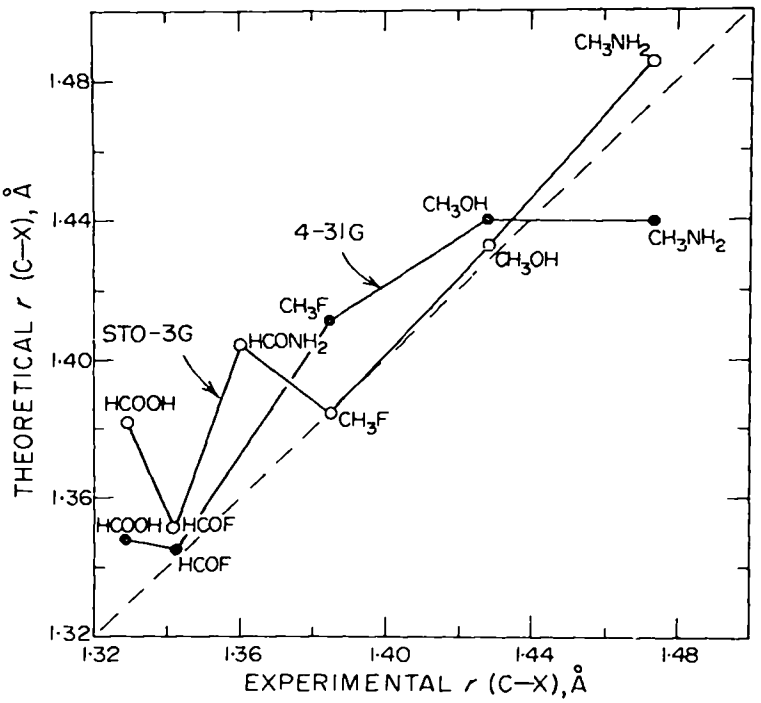


FIGURE 10. Experimental and theoretical CH_3-X and HCO–X bond lengths. The open and solid circles refer to STO-3G and 4-31G optimized bond lengths respectively. The 45° broken line corresponds to perfect agreement between experiment and theory.

Figure 10. The similarity and discrepancy between theoretically and experimentally determined values may also be seen in the table.

B. Acyl Halides

The only acyl halides that have been the object of *ab initio* investigations are the fluorides, since the other halides are not expected to give qualitatively different results, and are more difficult to handle computationally. The first calculations on formyl fluoride were reported[11] as early as 1963 in which the authors determined the effect of basis-set size on energies and the dipole moment. Preliminary geometry optimization also confirmed theoretically that the molecule was planar.

Basch and coworkers[12] have studied both the theoretical and experimental electronic excitation spectra of formyl fluoride. Their results, obtained by the virtual orbital technique with a double-zeta basis set plus atomic Rydberg functions, are compared to other results and the experimental values in Table 2. The Rydberg states were found to lie several eV above the lowest excited states, the triplet $n \rightarrow \pi^*$, triplet $\pi \rightarrow \pi^*$ and singlet $n \rightarrow \pi^*$. They also computed the highest occupied n- and π-orbital ionization potentials (IP)[13] to be 14.15 and 15.35 eV respectively.

Pople and coworkers studied formyl fluoride as one of a large number of molecules in a series of papers[14–18] which examined many properties using standard geometries[19] for all the compounds. Using the 4-31G basis set, the heat of

TABLE 2. Single (S) and triplet (T) excitation energies (eV) for formyl fluoride

Reference	Basis	S($n \rightarrow \pi^*$)	T($n \rightarrow \pi^*$)	S($\pi \rightarrow \pi^*$)	T($\pi \rightarrow \pi^*$)
12	DZ + R[a]	6.68	6.18	13.02	6.69
16	STO-4G + CI[b]	5.14	4.15	11.26	4.76
16	4-31G + CI[b]	5.97	5.24	10.32	5.00
8	STO-3G + CI[b,c]	5.00	–	–	–
8	STO-3G + CI[b,d]	5.22	–	–	–
8	STO-3G + CI[b,e]	5.58	–	–	–
22	GL + CI[f]	5.58	5.17	–	–
12	Experimental	5.64	–	9.43	–

[a] Double zeta plus atomic Rydberg functions.
[b] The limited CI included up to eight configurations.
[c] Standard geometry, Reference 19.
[d] Optimized geometry.
[e] Experimental geometry, Reference 24.
[f] Gaussian lobe plus CI (up to 400 configurations).

formation was calculated[15] to be −85.0 kcal/mole, in good agreement with the experimental value of −90.00 kcal/mole. Fluorine was also found to form a stronger bond with H—C=O than H—C=NH as the bond separation energies were 19.2 and 12.9 kcal/mole respectively. This result was rationalized in terms of the differing abilities of C=O and C=NH to accept π-electron donation from the F atom. While this qualitative conclusion may be correct, the numerical values computed within the SCF framework for the dissociation would incorporate a systematic error associated with the change of correlation energy.

Limited CI calculations using up to eight configurations have been performed[16,17] on the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions. The results were found to be very sensitive to the basis-set size and number of configurations included. The *cis* and *trans* isomers of HC(=NH)F were also studied[17] with singlet $n \rightarrow \pi^*$ excitation energies of 6.50 and 6.19 eV respectively. The same transition was predicted to occur at 5.40 eV for acetyl fluoride, while the experimental value is 6.04 eV.

Several authors have computed the dipole moment, and the results are presented in Table 3. Note that the experimental value[20] is 2.02 D.

Hehre, Radom and Pople[18] have performed STO-3G calculations on the planar conformation of benzoyl fluoride, but there are no experimental values for comparison of the results.

TABLE 3. Computed dipole moments of HCOF

Reference	Geometry	Basis	μ(D)
12	Exp[24]	DZ + R[a]	2.80
14	Std[19]	STO-3G	1.75
8	Opt[8]	STO-3G	1.52
22	Exp[25]	GL-CI[b]	2.60
20	Exp	Exp	2.02
26	Exp	Exp	1.99

[a] Double zeta plus atomic Rydberg basis set.
[b] Gaussian lobe basis set plus CI (400 configurations).

TABLE 4. Theoretical and experimental geometries of formyl fluoride

	Theoretical[8]	Experimental[25]	Experimental[24]
r(C=O) (Å)	1.210	1.185	1.181
r(C–F) (Å)	1.351	1.345	1.338
r(C–H) (Å)	1.108	1.082	1.095
∠OCF (degrees)	122.1	121.9	122.8
∠OCH (degrees)	125.6	110.2	127.3

Del Bene and coworkers[8] have optimized the geometry of formyl fluoride with the STO-3G basis set. The results agree well with the experimental geometry (see Table 4), except for the value of the OCH angle which varies widely experimentally[21]. The vertical ionization potentials for the highest occupied n- and π-type orbitals were found to be 10.45 and 11.14 eV respectively[13]. While the *IP*s were relatively insensitive to the geometry, the $n \rightarrow \pi^*$ excitation energies differed markedly, as can be seen from Table 2 which collects the results of many studies of the electronic excitations of HCOF.

Ha and Keller[22] have also studied the $n \rightarrow \pi^*$ excitation using a more complete CI (up to 400 configurations). They obtained values of 5.58 eV and 5.17 eV for the singlet and triplet $n \rightarrow \pi^*$ transitions respectively. Ha and Keller also computed a nuclear quadrupole coupling constant of 239.9 kHz for the deuterium of the formyl group.

Pople and coworkers[23] attempted to calculate the n.m.r. coupling constants for a series of molecules including HCOF. Despite encouraging results from semi-empirical studies the authors concluded that minimal basis sets 'do not appear promising for reproducing experimental magnitudes and trends'[23].

TABLE 5. Geometrical parameters for *cis* formic acid

Method [a]	r(C=O)[b]	r(C–O)[b]	r(O–H)[b]	∠OCO[b]	∠COH[b]	Reference
E	1.24	1.42	–	117	–	28
E	1.213	1.368	–	123.5	–	29
E	1.225	1.41	–	125	107	30
E	1.23	1.36	0.97	122.4	–	31
E	1.245	1.312	0.95	124.3	107.8	32
E	1.202	1.343	0.972	124.9	106.3	33
E	1.22	1.34	0.97	124.8	105.5	34
E	1.217	1.361	0.984	123.4	107.3	27
E	1.228	1.317	0.974	125.0	106.8	35
T[c]	1.214	1.386	0.991	123.7	104.8	8
T[d]	1.215	1.332	0.97	–	114	36
T[c]	1.214	1.378	0.991	124.2	105.4	37
T[e]	–	–	0.990	–	104.7	37

[a] E and T refer to experimental and theoretical determinations respectively.
[b] Bond lengths are measured in Angstroms and angles in degrees. Assumed values are denoted by dashes and are not shown.
[c] Using STO-3G basis set.
[d] Using a 9*s*4*p*/4*s* basis set contracted to 4*s*2*p*/2*s*, but optimizing each coordinate independently starting each time with the same (experimental) geometry[27], i.e. not a simultaneous or cyclic minimization of the energy.
[e] Geometry predicted by a hypersurface $E = E(r_{OH}, \alpha_{COH}, \tau_{OCOH})$ fitted to the SCF points.

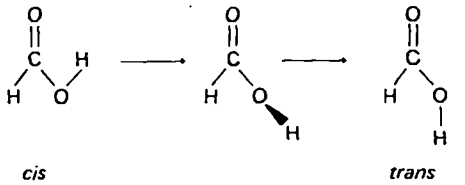
TABLE 6. Formic acid *cis–trans* energy difference and barrier to rotation

Method [a]	ΔE^b(kcal/mole)	ΔE_B^c(kcal/mole)	Reference
E	2.0	10.9 (98°)	38
E	–	13.4	39
E	–	17	32
E	> 4	–	40
T	8.1	–	41
T	9.46	14.20	42
T	8.1	13.0	43
T	6.30	12.2 (97°)	44
T	4.8	12.34	45
T	4.5	9.6	37
T[d]	4.4	9.6 (90°)	37

[a] E and T refer to experimental and theoretical determinations respectively.
[b] *Cis–trans* energy difference.
[c] Barrier height, from *cis* conformation. The angle at the transition state was assumed to be 90° for the theoretical results unless an optimized value is indicated in parentheses.
[d] These values calculated from a hypersurface fitted to the SCF energies.

C. Acids and Esters

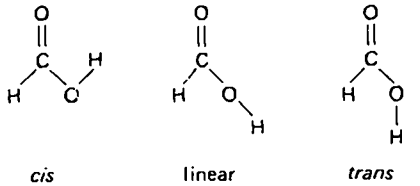
The most stable conformation of formic acid (2) occurs with the hydroxyl H *cis* to the carbonyl O. Tables 5 and 6 summarize the many experimental and theoretical determinations of the geometry, *cis–trans* energy difference and the barrier to OH rotation. The agreement of the geometrical parameters is good,



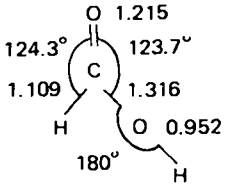
(2)

although the carbonyl bond is a little short, and the C—O bond is predicted to be too long compared with the more recent experimental bond lengths with the exception of Reference 27 (see also Figure 10 and Table 1). The results for the energy difference and barrier are not conclusive, as both the experimental and theoretical values show considerable scatter.

The barrier to the in-plane conversion of the *cis* to the *trans* conformer via a linear COH transition state (inversion at oxygen) has been calculated[37] to be

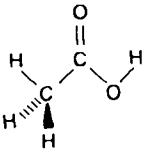


53.8 kcal/mole from an analytic hypersurface of energy as a function of the O—H bond length, C—O—H angle and the hydroxyl torsional angle. The entire structure was optimized directly, yielding the same energy barrier, with a shortening of the C—O bond length as shown:



Both the direct optimization and the fitted hypersurface show a shortening of the linear OH bond to 0.95 Å compared with the 0.99 Å of the *cis* and *trans* conformers.

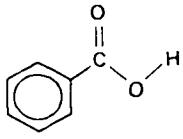
The *cis–trans* energy difference for acetic acid has been computed twice, with values of 7.67[44] and 7.24[45] kcal/mole respectively. The OH rotation barrier[45] was 13.18 kcal/mole. The most stable conformer occurs with a C—H bond of the methyl group eclipsed with the carbonyl group (3). The theoretical barrier to



(3) *cis–cis*

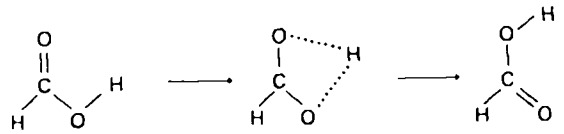
methyl group rotation has been computed as 0.31[44] and 1.10[45] kcal/mole, while 0.48 kcal/mole has been found experimentally[46].

The *cis* form of benzoic acid (4) was calculated[18] to be 6.92 kcal/mole more stable than the *trans* conformation, and the barrier to rotation of the entire COOH group, with respect to the plane of the phenyl ring, was 5.76 kcal/mole.

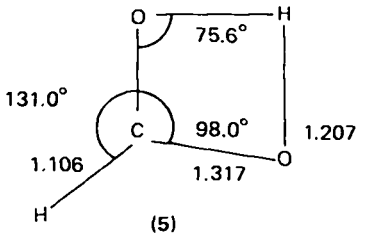


(4) *cis*

The barrier to in-plane tautomerization of formic acid by the process:



has been calculated as 74.2[58] and 59.1[37] kcal/mole using optimized geometries for both the stable species and the transition state. The geometry[37] of the transition state 5 which has C_{2v} symmetry is shown below.



(5)

Several authors[14,22,43,47] have calculated the dipole moment of formic acid. The results in best agreement with the experimental value[48] of 1.415 D were 1.420 D[47] and 1.419 D[22], which were calculated from CI wave functions. The dipole moment of benzoic acid was computed[18] to be 1.08 D, while the experimental value is 1.72 D. Ha and Keller[22] also calculated a nuclear quadrupole coupling constant of 225.7 kHz for the deuterium of the formic acid carbonyl group.

Clementi and coworkers[36] have calculated *ab initio* some of the diagonal and a few of the off-diagonal force constants of formic acid and its dimer. As seems to be the usual result for *ab initio* (or semiempirical) force constants, they are overestimated but in satisfactory agreement with the experimental values. Vibrational frequency shifts that occur upon dimerization are readily explained in any case.

The electronic excitations of formic acid have also been studied by several groups, and the results are presented in Table 7. Demoulin[49] included atomic Rydberg functions in the basis set and found that the four lowest energy singlet excitations were $n \rightarrow \pi^*$ (5.24 eV), $n \rightarrow 3s$ (8.14 eV), $\pi \rightarrow 3s$ (8.67 eV) and $\pi \rightarrow \pi^*$ (9.64 eV). While all the singlet $n \rightarrow \pi^*$ excitation energies agree well with the experimental values, the singlet $\pi \rightarrow \pi^*$ transition energy is consistently overestimated.

All authors are agreed that the triplet $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ excitations lie very close in energy. Demoulin[49] also computed two triplet Rydberg states to occur at 7.98 eV ($n \rightarrow 3s$) and 8.36 eV ($\pi \rightarrow 3s$).

The singlet $n \rightarrow \pi^*$ transition of acetic acid is predicted[17] to occur at 5.20 eV, compared with an experimental value of 5.89 eV.

The Koopmans' Theorem[13] ionization potentials (*IP*), summarized in Table 8, do not resolve the question of whether the highest occupied molecular orbital

TABLE 7. Electronic transition energies (eV) for singlet and triplet excitations of formic acid

Method	S($n \rightarrow \pi^*$)	S($\pi \rightarrow \pi^*$)	T($n \rightarrow \pi^*$)	T($\pi \rightarrow \pi^*$)	Reference
T	5.90	9.52	5.47	5.86	47
T	5.36	10.72	4.53	4.02	16
T	5.22[b]	–	–	–	8
T	5.38[c]	–	–	–	8
T	5.61[d]	–	–	–	8
T	5.46	–	5.11	–	22
T	5.24	9.64	4.60	4.80	49
E	5.7	8.3	–	~4.3	50

[a]T and E refer to theoretical and experimental results respectively.
[b]Standard geometry.
[c]Optimized geometry.
[d]Experimental geometry.

TABLE 8. Ionization potentials (eV) for formic acid

Method[a]	*IP*(*n*)	*IP*(π)	Reference
T	10.7	10.3	41
T	12.7	13.2	42
T	12.3	12.1	51
T	9.71[b]	9.68	8
T	9.83[c]	9.93	8
T	9.82[d]	9.93	8
T	11.51	12.50	49
E	11.33		52

[a] T and E stand for theoretical and experimental results respectively.
[b] Standard geometry.
[c] Optimized geometry.
[d] Experimental geometry.

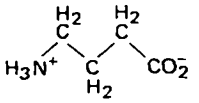
(HOMO) is of *n* or π type. All results indicate that the *IP*s are close and Del Bene and coworkers[8] have shown that the results are strongly dependent on relatively small changes in the molecular geometry.

Peyerimhoff[53] has computed many electronic states of the formate ion with a limited CI and compared the results with spectra of the isoelectronic systems ozone (O_3) and nitrite ion (NO_2^-), as experimental data on $HCOO^-$ seem scarce. She has also found an optimum ground-state OCO angle of 128°, in good agreement with the experimental[7] range of 124–127°. The two lowest doubly-excited states are predicted to have OCO angles of 160° and 73°.

Calculations by Basch and coworkers[12] using the virtual orbital technique have confirmed the singlet $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition energies to be about 7.4 and 10.8 eV respectively (6.7 and 10.8 eV from Reference 53). The triplet $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ excitation energies were 6.9 and 5.81 eV, but singlet and triplet $n' \rightarrow \pi^*$ transitions from the next lowest occupied MO were also computed to fall near 7 eV.

Peyerimhoff and Buenker[47] have reexamined $HCOO^-$, adding a bare positive charge with no accompanying atomic orbitals to represent the non-interacting counter-ion, and to make the molecule neutral. The OCO angle was predicted to be 125°, compared with an angle of 104° for the transition state 5 of the formic acid tautomerization when the migrating H orbitals were included in the basis set (cf. the OCO angle of 98° for the completely optimized structure[37]).

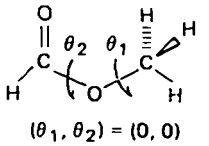
The structure of the zwitterionic form of γ-aminobutyric acid (6) was studied by Pullman and Berthod[54] with the result that a highly folded form allowing interaction of the changed ends was more stable than the fully extended form (all C—C bonds *trans*) by some 44 kcal/mole. The sites of hydration were also discussed.



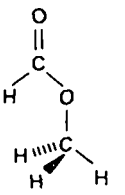
(6)

Methyl formate (7) is the only ester that has been treated by *ab initio* techniques. Radom and coworkers[44] found the most stable conformation to have the

methyl group *cis* to the carbonyl, but a methyl C=H bond *trans* to the C=O bond [the (0, 0) conformation], in agreement with the experimental structure.[55] There have been two other studies of this system[45,56], and the results are summarized in Table 9. The discrepancies in the theoretical values are probably due to the different geometries used for the (0, 0) conformer, with the optimized geometry calculation[56] being closest to the experimental results.



(7)



(0,180)

TABLE 9. Conformational energy differences and barriers to rotation for methyl formate (kcal/mole)

Method[a]	$\Delta E(\theta_2)^b$	$\Delta E_B(\theta_2)^c$	$\Delta E_B(\theta_1)^d$	Reference
T	5.56	—	4.72	44
T	3.68	11.36(90°)[e]	3.68	45
T[f]	2.65	7.83(103°)	1.41[g]	56
E	—	—	1.190	55
E	—	—	1.165	57

[a] T stands for theoretical, E for experimental results.
[b] *Cis*(0, 0)–*trans*(0, 180) energy difference.
[c] Energy barrier for θ_2 rotation about the ester bond (angle of saddle point in parentheses).
[d] Energy barrier for θ_1 rotation of the methyl group.
[e] Assumed.
[f] These values obtained from a surface fitted to the SCF energy values.
[g] For the *trans*(0, 180) conformation the barrier to methyl group rotation was 0.87 kcal/mole.

D. Amides

Amides have been studied extensively, as the amide linkage is the fundamental functional group of proteins. Formamide, the simplest molecule of this class (i.e. the one with the smallest number of electrons), has been investigated most often, but *N*-substituted amides have frequently been chosen as a better model for proteins. Such substituted amides (at C or N) will be discussed later in this section.

The gas-phase structure of formamide has been determined four times in the last twenty years and there is some disagreement concerning the geometry. Costain and Dowling[59] found that the N atom was non-planar to the extent of twisting the two hydrogens 7° and 12° from the HCON plane.

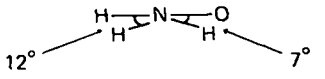


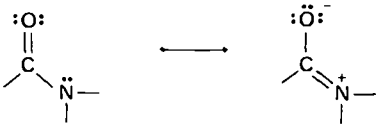
TABLE 10. The geometry of formamide

Method[a]	r(C=O)[b]	r(C–N)[b]	r(N–H)[b]	⟨OCN[b]	Reference
T	1.212	1.363	0.955	–	63
T[c]	1.218	1.403	1.014	124.3	8
T[c]	1.218	1.404	1.014	124.2	64
E	1.243	1.343	0.995	123.6	60
E[d]	1.193	1.376	1.008	123.8	59
E	1.212	1.368	1.027	125.0	61
E	1.219	1.352	1.001	124.7	62

[a] T stands for theoretical, E for experimental.
[b] Bond lengths in Angstroms, angles in degrees. The N–H bond length given is the average of the two values.
[c] N atom assumed planar.
[d] N atom found to be non-planar.

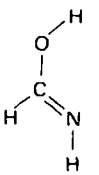
All other determinations[60-62] reported in Table 10 have found the geometry to be planar within the experimental error bounds. Large basis-set calculations[63] including *d* functions have failed to resolve the question. Table 10 also presents the *ab initio* optimized structures of formamide. Note the long STO-3G optimized C—N bond length[8,64].

The barrier to rotation about the C—N bond has been calculated to be 19.4–21.7[63], 24.7[44], 19.7[65], 20.3[45] and 18.2[66] kcal/mole with various geometries and basis sets. All the values agree very well with the experimental results, namely 16.8–21.3[67], 18[68] and 19.2–19.7[69] kcal/mole, indicating that this property may be estimated reliably with even small basis sets. Of course, the large energy barrier to rotation is ascribed to the partial double-bond character of the amide linkage, as in the following resonance structures:



Good dipole moments, however, are not in general obtained from small basis set calculations except by coincidence, as may be seen from Table 11. The table includes details of the theoretical methods used as well as the total energies obtained. It is clear that the $|\mu|$ varies non-monotonically with the quality of the calculations as measured by E. The $|\mu|$ results are plotted in Figure 6 and the directions of the dipole moment vectors $\vec{\mu}$ are shown in Figure 7. The best agreement with the experimental value[60] of 3.71 D was calculated from a Valence Bond wave function[66] (3.79 D).

Other tautomers and isomers of $HCONH_2$ have been studied including the iminol form, formamidic acid (8), which was computed to be 22.6[70] and



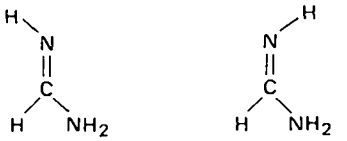
(8)

TABLE 11. Total energy and dipole moment of formamide

Method[a]	Basis-set size[b]	$-E$(hartrees)	$\mid \mu \mid$ (D)[c]	$\hat{\mu}$(degrees)[d]	Reference
T(SCF)	36(87)	168.8661	4.95	165.7	71
T(SCF)	36(87)	168.8648	4.39[e]	166.4	71
T(SCF)	59(59)	168.5259	4.15	169.3	73
T(SCF)	36(87)	168.872	4.29[e]	167.5	70
T(SCF)	60(120)	168.91731	4.39	167.1	63
T(SCF)	18(54)[f]	[g]	3.34	160.0	14
T(SCF)[h]	15(15)	143.7746	3.91[e]	161.1	65
T(SCF)	18(54)[f]	166.67192	3.02[e]	[g]	72
T(SCF)	33(72)[i]	[g]	4.7	[g]	72
T(SCF)	18(54)[f]	[g]	2.64	[g]	8
T(SCF + CI)	36(90)	168.8851	4.48	[g]	22
T(VB)[j]	36(84)	168.94352	3.79	166.3	66
T(GL + CI)[k]	55(106)	169.2306	4.1	163.0	74
E[l]	–	–	3.714	163.2	60

[a] T stands for theoretical, E for experimental results.
[b] Total number of contracted basis functions. The number of primitive basis functions is in parentheses.
[c] Planar geometry at N unless otherwise noted.
[d] Direction is measured in degrees from the CO bond towards the CN bond using the C atom as the origin. The dipole-moment vector points from negative to positive charge.
[e] Pyramidal geometry at N. The small out of plane component of μ has been neglected.
[f] STO-3G basis set.
[g] Not reported.
[h] Floating Spherical Gaussian Orbital (FSGO) basis set.
[i] 4-31G basis set.
[j] Valence bond calculation.
[k] Gaussian lobe plus CI.
[l] Determined from the Stark effect on the microwave spectrum.

23.0[15] kcal/mole less stable than formamide. Calculations have been performed[70] on the excited states of the isomers as well.



cis *trans*

(9)

Pople and coworkers[16] included $HC(NH)NH_2$ (9) as one of a series of compounds, and concluded that the *cis* isomer is 2.94 kcal/mole more stable than the *trans*. They also calculated[7] the singlet $n \rightarrow \pi^*$ transition energies of $HC(=NH)OH$ and $HC(=NH)NH_2$ to be 6·72 and 6.85 eV.

Several workers have reported the Koopmans' Theorem[13] ionization potentials of the highest occupied n and π orbitals. All agree the highest occupied orbital is of π-type (unlike the case of formic acid, see Section III.C) and the values of 11.5[73], 11.32[12], 8.38[8] and 11.5[74] eV are in fair agreement with the experimental value of 10.2 eV[75], as is usual when Koopmans' Theorem is applied.

The computed singlet and triplet electronic excitation energies are presented in Table 12, where the lowest singlet excitation is seen to be $n \rightarrow \pi^*$ near 5.7 eV, with

TABLE 12. Singlet (S) and triplet (T) electronic transition energies (eV) for formamide

Method[a]	$S(n \rightarrow \pi^*)$	$S(\pi \rightarrow \pi^*)$	$T(n \rightarrow \pi^*)$	$T(\pi \rightarrow \pi^*)$	Reference
T	6.42	10.41	5.88	5.46	71
T	6.75	11.09	6.15	6.64	73
T	6.89	10.50	6.36	6.06	12
T	7.05	10.50	6.31	6.66	70
T[b]	5.46	10.70	4.53	4.07	16
T[b]	5.49	–	–	–	8
T[c]	5.22	–	5.32	–	22
T[d]	5.65	–	5.39	6.19	66
T[c]	5.70	8.5	5.38	5.81	74
E	5.65	7.32	–	–	71
E	5.8	7.3	–	–	12
E	–	–	5.30	~6.6	76

[a]T is theoretical, E is an experimental determination.
[b]Limited CI (8 configurations) calculation.
[c]Large CI (200–400 configurations) calculation.
[d]Valence bond + CI calculation.

excellent agreement with experiment being achieved by limited CI techniques. Even an extensive CI calculation[74], however, still places the singlet $\pi \rightarrow \pi^*$ transition at least 1 eV too high in energy (this result also occurred for formyl fluoride and formic acid – see Sections III.B and III.C). While the lowest triplet $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ excitations are found to lie close to the singlet $n \rightarrow \pi^*$ transition, the exact ordering varies considerably, with the recent, more extensive CI Calculations[66,74] favouring the order $T(n \rightarrow \pi^*)$ occurring at 5.4 eV, $S(n \rightarrow \pi^*)$ at 5.7 eV followed by $T(\pi \rightarrow \pi^*)$ near 6 eV. This agrees well with the experimental electronic spectrum[12,71,76] (see Table 12). Several singlet transitions to atomic Rydberg states were calculated by various authors[12,71,74] to lie between the $S(n \rightarrow \pi^*)$ and $S(\pi \rightarrow \pi^*)$ excitations.

Harding and Goddard[66] investigated both planar and twisted (the plane of the NH_2 group at 90° to the HCO plane) geometries for all the states studied. While the $T(\pi \rightarrow \pi^*)$ state preferred a planar geometry, both $n \rightarrow \pi^*$ states were found to be twisted with barriers to rotation about the C—N bond (through a planar structure) of approximately 6 kcal/mole. Baird and Kathpal[77], using a minimal STO-3G basis set, found the same structural preferences for the various states. With their basis set, the triplet states were separated by 23.6 kcal/mole using the fixed twisted geometry of Harding and Goddard[66], but the difference was reduced to just 8.0 kcal/mole when both triplet-state geometries were optimized. The barrier to C—N bond rotation was also reduced, from 14 to 5 kcal/mole. This work indicates that the $T(n \rightarrow \pi^*)$ and $T(\pi \rightarrow \pi^*)$ states may be very close in energy, and also the importance of optimizing the excited state geometries as well as that of the ground state.

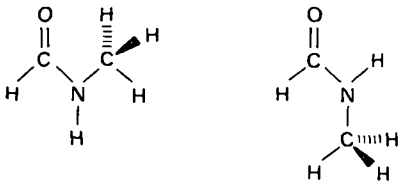
Other properties of formamide that have been computed include the bond energy[78], the ^{13}C and ^{1}H n.m.r. shifts[79,80], and the nuclear quadrupole coupling constants[22] and moments[47]. Janoschek[81] has calculated a potential energy surface for the NH_2 stretching modes, and computed the theoretical frequencies of vibration from the force constants.

Two *C*-substituted amides, $RCONH_2$, have been studied: acetamide (CH_3CONH_2) and benzamide ($PhCONH_2$). For the latter compound, Pople and coworkers[18] found that the conformation with the plane of the amide group twisted

30° with respect to the phenyl plane was 0.79 kcal/mole more stable than the all-planar structure. The barrier to rotation through an orthogonal conformer was computed to be 2.89 kcal/mole. These results are in agreement with experiment, which gives a 26° angle of rotation for the minimum energy form.

Radom and coworkers[44] examined acetamide and found the lowest energy form to have a methyl H eclipsing the carbonyl group (cf. acetic acid in the previous section). The calculated barrier to methyl rotation was only 0.3 kcal/mole. A barrier of 1.16 kcal/mole was computed by Perricaudet and Pullman[45], who also found a barrier to rotation about the C—N bond of 20.14 kcal/mole (16.7–17.3 experimentally[82]). A singlet $n \rightarrow \pi^*$ transition energy of 5.57 eV has been calculated[17], compared to the experimental value of 5.4 eV[50].

Turning to *N*-substituted amides, the lowest energy conformation of *N*-methylformamide (NMF) (**10**) was reported[44] to have the methyl group *cis* to the carbonyl group, in agreement with experiment[83]. The *trans* form was predicted to lie 2.7 kcal/mole higher and to have the methyl C—H bond now eclipsing the C—N bond. The barrier to CH_3 group rotation was 1.1 kcal/mole for the *cis* form, and 0.3 kcal/mole for the *trans*.

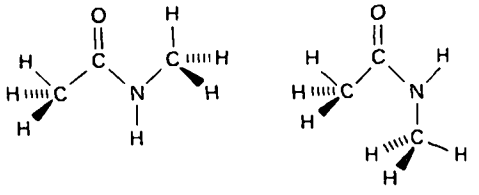


cis *trans*

(10)

These results for NMF were confirmed by Perricaudet and Pullman[45], who computed the *cis–trans* energy difference to be 1.83 kcal/mole, compared with experimental values of 1.4[84] and 1.6[85] kcal/mole. The barrier to methyl rotation was 0.86 kcal/mole for the *cis* conformer, and that to rotation about the C—N bond 22.54 kcal/mole. The corresponding experimental values for energy of activation of C—N bond rotation are 22–25.6[84], 20.4–21.6[85] and 19.0[86] kcal/mole.

N-methylacetamide (NMA) (**11**) was studied by Shipman and Christoffersen[65], using floating spherical gaussian orbitals (FSGO). The lowest energy was obtained for a conformation with the *N*-methyl group *cis* to the carbonyl group, a *C*-methyl group hydrogen eclipsing the CO group, and an *N*-methyl group hydrogen eclipsing the C—N bond. This C—N bond conformation was also found experimentally[87].



cis *trans*

(11)

The *trans* form (*N*-methyl group *trans* to CO group) was computed to be 3·66 kcal/mole less stable. The experimental value is 2.8 kcal/mole[85]. Note that the conformational behaviour of the *N*-methyl group upon rotation about the C—N bond is opposite to that of NMF. The calculated barriers to *C*- and *N*-methyl rotation for

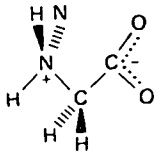
cis-NMA were 1.10 and 0.69 kcal/mole respectively (2.76 and 1.97 kcal/mole for *trans*-NMA).

E. Biological Molecules

One class of biological molecules of great importance is the amino acids. Glycine, $^{+}NH_3CH_2COO^{-}$, and polypeptides of glycine have been the subject of several *ab initio* investigations. Ryan and Whitten[88] performed calculations on the planar conformers of the glycine and glycylglycine zwitterions, and found that no major redistribution of electronic charge occurs upon dimerization (formation of the peptide bond).

Shipman and Christoffersen[89] studied the single-strand mono- through penta-peptides of glycine, in several conformations including the fully extended chain and the α-helix. For all peptides, the fully extended conformation was favoured over all of the folded conformations, but interchain hydrogen bonds of moderate strength (~ 5 kcal/mole) could reverse the calculated stabilities.

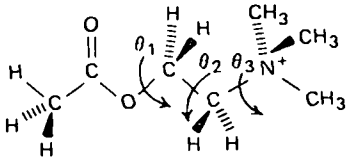
The same authors computed[90] a conformational energy surface for the glycine zwitterion. The absolute minimum corresponded to the conformation **12**, which is in agreement with experiment. The calculated barrier to NH_3^+ rotation was 1.5 kcal/mole, and to CO_2^- rotation was 10.1 kcal/mole. The dipole moment was computed to be 13.33 D, in good agreement with the experimental values of 13.3 D and 15.0 D (Ryan and Whitten[88] calculated a value of 12.17 D).



(12)

Almlof and coworkers[91] compared the SCF electron density distribution for glycine to that measured by X-ray and neutron diffraction. The agreement was 'qualitatively most encouraging'[91].

Acetylcholine, a molecule important in the transmission of nerve impulses, has been studied by Genson and Christoffersen[92] using a molecular fragments approach. The fully extended (180°, 180°, 180°) conformer (**13**) was found to be more stable than any of the folded (*gauche*) conformations by 10–20 kcal/mole, in contrast to previous semiempirical calculations and crystal structures which favour conformations near (180°, 80°, 180°).



(13)

STO-3G calculations by Port and Pullman[93], however, predict the *gauche* (180°, 60°, 180°) conformation to be 3 kcal/mole more stable than the all-*trans* (180°, 180°, 180°) conformation, in line with the previous semiempirical studies. They also found that allowing a small change (20°) in the θ_3 angle as θ_2 nears 60° (to

reduce the interaction of the ester oxygen with the cationic head) led to a 4 kcal/mole reduction in the energy of the *gauche* conformer when using Christoffersen's geometry[92]. From a potential energy surface[94] as a function of θ_1 and θ_2 (θ_3 was fixed at 180°), the authors found the absolute minimum to be (150°, 60°) which is a *gauche* conformation for the C—C bond. The fully extended form (180°, 180°) was 4 kcal/mole less stable.

IV. CHEMICAL PROPERTIES

A. Protonation, Deprotonation and Proton Transfer

Consecutive protonation and deprotonation reactions allow one to relate the acidity and basicity of compounds:

$$A:^- \underset{1'}{\overset{1}{\rightleftharpoons}} AH \underset{2'}{\overset{2}{\rightleftharpoons}} AH_2^+$$

Step 1 measures the basicity of A^-.
Step 1' measures the acidity of AH.
Step 2 measures the basicity of AH.
Step 2' measures the acidity of AH_2^+.

The energy changes in reactions 1 or 2 are given by *PA*, the proton affinity of A^- or AH with a positive or negative sign according to the thermodynamic convention.

The proton affinity of A^- is defined:

$$\Delta E(1) \equiv PA(A^-) = E(AH) - E(A^-) \tag{51}$$

and for the reverse step the energy of separation is the negative of the proton affinity:

$$\Delta E(1')) = -PA(A^-) \tag{52}$$

Correspondingly the proton affinity of AH is given as:

$$\Delta E(2) \equiv PA(AH) = E(AH_2^+) - E(AH) \tag{53}$$

and an analogous relationship holds for the second reverse reaction:

$$E(2') = -PA(AH) \tag{54}$$

It perhaps should be noted that in a protonation process a chemical bond is formed, hence the *PA* value is always negative for a neutral or negatively charged compound. Consequently for deprotonation where a bond is disrupted the energy value has a positive sign since it is equal to the negative of the *PA*.

Proton affinity is related to the dissociation energy (*D*), the ionization potential (*IP*) of hydrogen and the electron affinity (*EA*) of A as shown in Figure 11, or mathematically:

$$-PA(A^-) = D + IP(H) + EA(A) \tag{55}$$

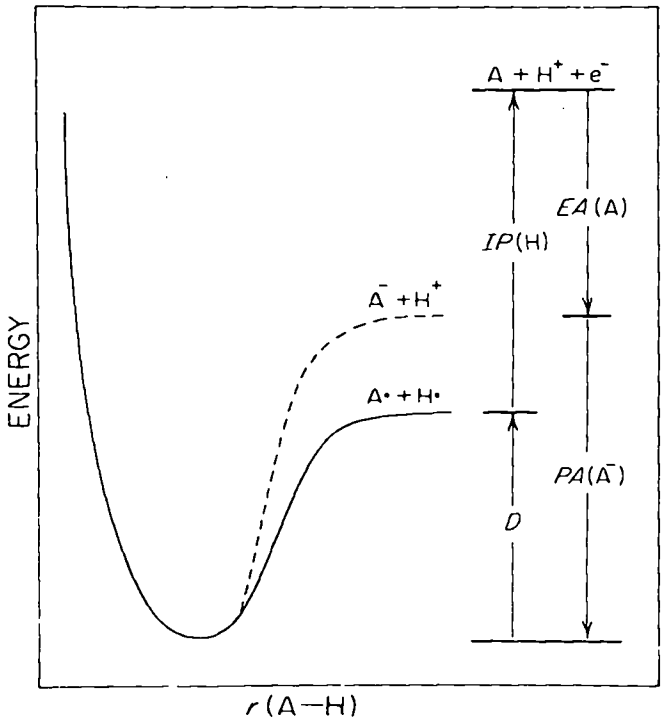
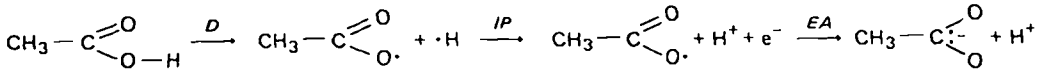


FIGURE 11. The relationship between the proton affinity (*PA*), dissociation energy (*D*), ionization potential (*IP*) and the electron affinity (*EA*).

In the case of a carboxylic acid the above relationship has the following explicit form:



$$D = 110.0$$
$$IP = 313.8$$
$$D + IP = 423.8$$
$$EA = -78.2$$
$$-PA = 345.6 \text{ kcal/mole}$$

Thus the proton affinity of acetate ion is −345.6 kcal/mole and its negative value (i.e. +345.6 kcal/mole) is the measure of the acidity of CH_3—COOH.

Yamdagui and Kebarle[95] determined the intrinsic acidities of carboxylic acids from gas-phase acid–base equilibria. On the basis of their measurements[96] one can rank the acidities of carboxylic acids (the negative of the carboxylate anion's *PA*) as in Table 13 with respect to the hydrogen halides starting with the least acidic (HF) towards the most acidic (HI).

There are a number of points to be noticed. First of all HCOOH does not quite fit into the homologous series. Secondly increasing chain length (from acetic acid to

TABLE 13. Experimental gas-phase acidities

Molecule	Acidity[a] (kcal/mole)
HF	370.1
CH_3COOH	345.4
CH_3CH_2COOH	344.4
$CH_3CH_2CH_2COOH$	343.5
HCOOH	342.4
HCl	333.8
$ClCH_2COOH$	332.8
$Cl_2CHCOOH$	325.8
HBr	323.8
HI	314.5

[a]Acidity is the negative of the proton affinity.
All values from Reference 95.

butyric acid) alters the acidity only slightly. Thirdly, successive chlorination (from acetic to dichloroacetic acid) makes a fairly appreciable increase in the acidity (i.e the lowering of the *PA*).

On turning to the basicity of carboxylic acids we need to have the proton affinity of the following protonation:

$$RCOOH + H^+ \rightarrow RCOOH_2^+$$

The experimental *PA* values[97] shown in Table 14 indicate the relative basicities of a few selected carboxylic acids. These proton affinities may be calculated as differences of molecular energies as shown for the formic acid case by Figure 12.

Clearly the experimental *PA* values from different sources are not identical but they are close enough to each other to see that proton affinities are computable within the SCF framework. As far as the accuracy is concerned it needs to be emphasized that even the experimental values carry a high degree of uncertainty. For example the following four reported *PA* values of HCOOH spread over a range of 17 kcal/mole: -162[98], -166[99], -175[100], -179[101].

TABLE 14. Experimental basicities of some carboxylic acids

Acid	−Proton affinity[a] (kcal/mole)
HCOOH	175
CH_3COOH	188
CH_3CH_2COOH	190
F_3CCOOH	167

[a]Reference 97.

Besides energetics there are stereochemical questions associated with protonation. One of the most important questions is the site of protonation. In the case of formate ion both oxygen atoms are equivalent, thus there is no chance for the formation of more than one tautomer. Directly the opposite is the case of formic acid (Scheme 1).

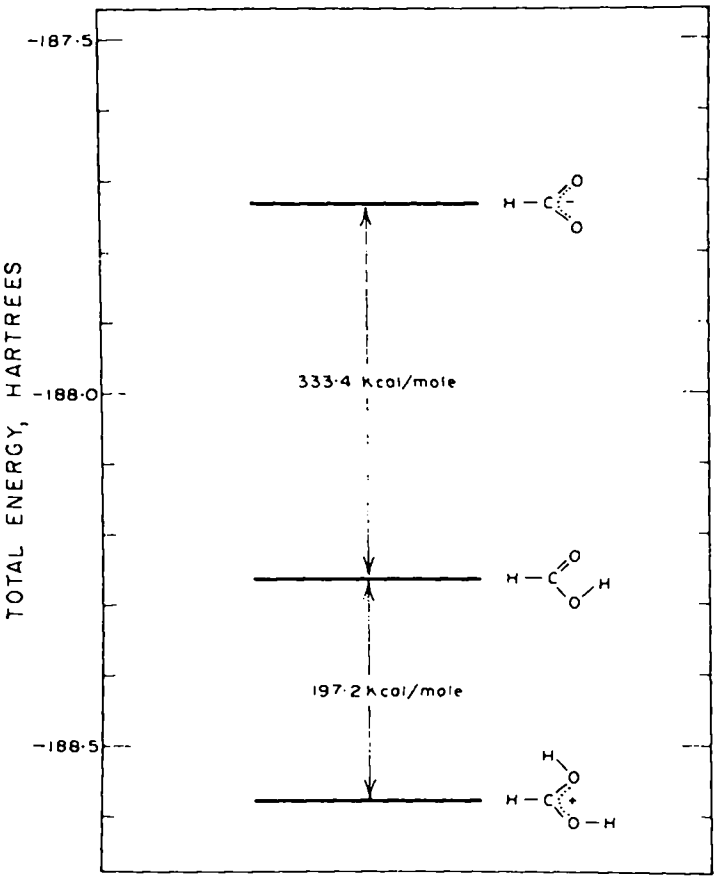
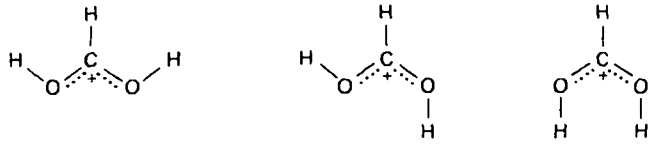


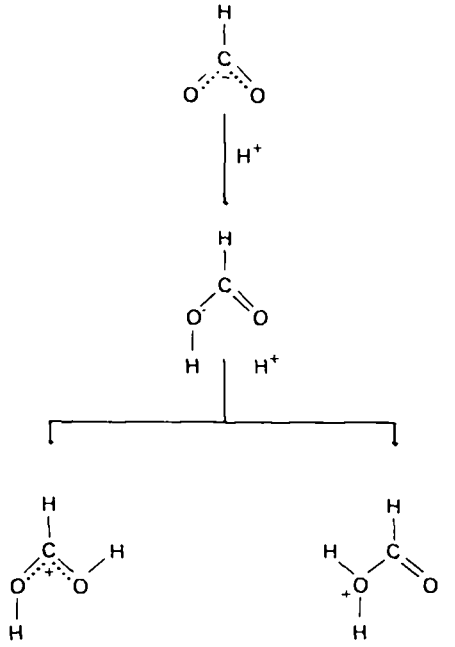
FIGURE 12. Computed proton affinities (kcal/mole) of formate ion to give *cis* formic acid, and *cis* formic acid to give the *cis–trans* protonated acid. Reproduced with permission from A. C. Hopkinson, K. Yates and I. G. Csizmadia, *J. Chem. Phys.*, 52, 1784 (1970).

The hydroxy-protonated tautomer of formic acid is less stable than the carbonyl-protonated tautomer by some 25 kcal/mole. However, within the carbonyl-protonated tautomer (**14**) there are three conformations. They differ in the orientation of the two hydroxyl protons relative to the C–H proton. The computed relative energies[102] of these four species are shown in Figure 13.



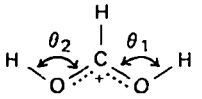
cis–cis *cis–trans* *trans–trans*

(14)



SCHEME 1.

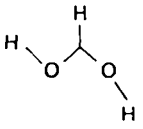
One way to interconvert the carbonyl-protonated conformers is through in-plane inversion at the oxygen atoms. This mode of interconversion is characterized by two bond angles θ_1 and θ_2:



The stable conformations occur for θ_1 and θ_2 near 120° and 240°. This leads to four minima:

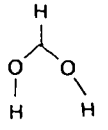
	θ_1	θ_2	
cis–cis	120°	120°	(min_2)
cis–trans	120°	240°	(min_1)
trans–cis	240°	120°	(min_1)
trans–trans	240°	240°	(min_3)

of which the second and the third are equivalent. These minima must be connected by two different transition states:



TS_1

($\theta_1 = 180°, \theta_2 = 120°$)



TS_2

($\theta_1 = 180°, \theta_2 = 240°$)

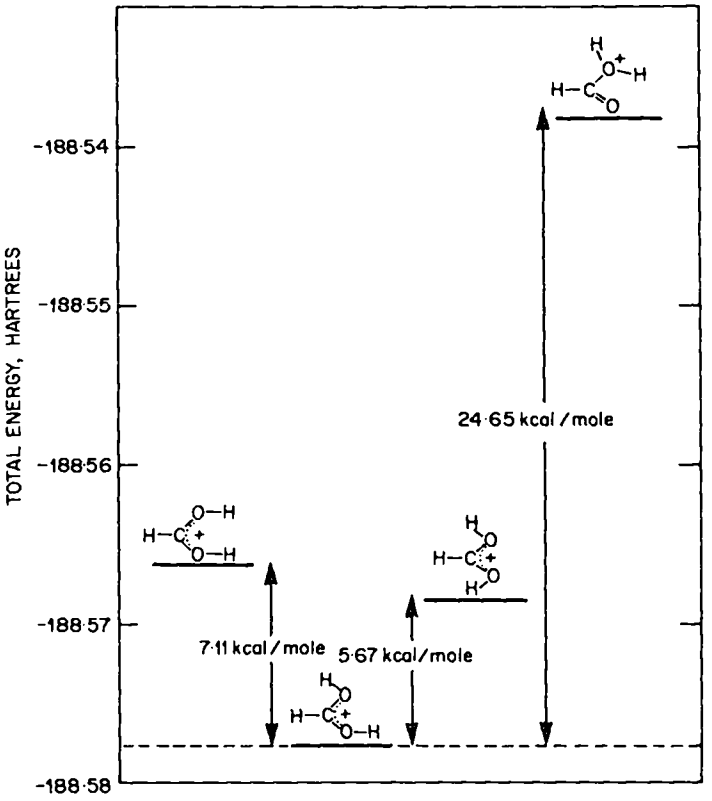


FIGURE 13. Computed total energies (hartrees) and relative stabilities (kcal/mole) of the conformers of protonated formic acid. Reproduced with permission from A. C. Hopkinson, K. Yates and I. G. Csizmadia, *J Chem. Phys.*, 52, 1784 (1970).

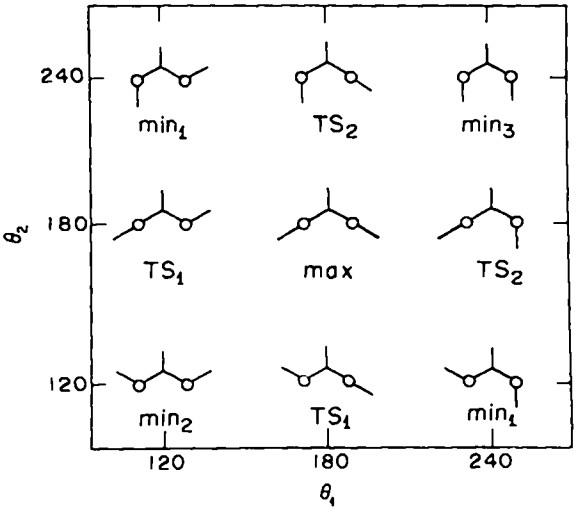
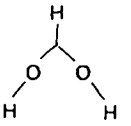


FIGURE 14. Topological map of the planar forms of protonated formic acid, showing the minima (stable species), saddle points (transition states) and the central maximum.

and all of these surround a maximum:



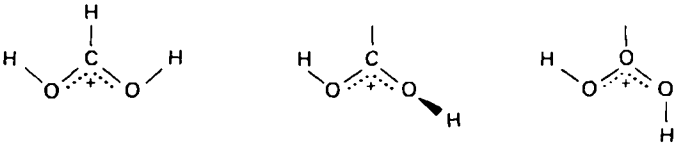
max

($\theta_1 = \theta_2 = 180°$)

Ros[41] computed TS_1 to lies about 22.8 kcal/mole above the lowest minimum, min_1, while the maximum was found to be about 37.7 kcal/mole above the absolute minimum, min_1. The topology of this surface (equation 56) is shown in Figure 14.

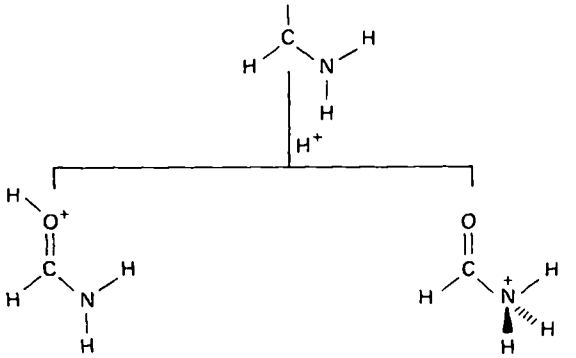
$$E = E(\theta_1, \theta_2) \tag{56}$$

Interconversion of these carbonyl-protonated species may also be achieved by rotating the C–OH bonds. For example the *cis–cis* conformers may be changed to the *cis–trans* conformer through a 90° rotation of the C–OH bond leading to a non-planar transition state (TS_3) which is 13.5 kcal/mole above the lowest minimum (min_1)[41].



min_2 TS_3 min_1

Turning to the protonation of formamide, the first question is the site of protonation. There are two possibilities: *O*-protonation and *N*-protonation. A number of papers[103] dealing with the problem reported computed proton affinities indicating that *O*-protonated formamide is more stable than the *N*-protonated tautomer (see Figure 15) by some 6 kcal/mole.



Although the observation that the *O*-protonated tautomer is more stable than the *N*-protonated one is believed to be significant, the numerical values of the proton affinities are probably too large due to the use of a moderate basis set and limited geometry optimization. Nevertheless it should be emphasized that there are no experimental proton affinity values available for formamide. The only way to make an estimate is to compare an isoelectronic series. There are a number of

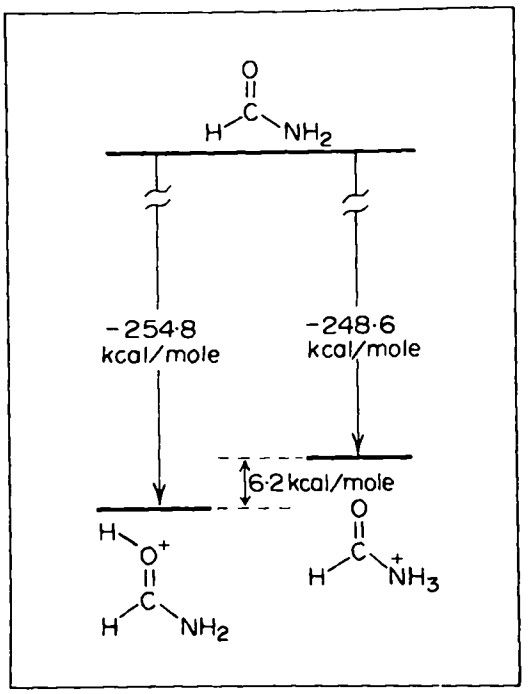
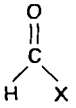


FIGURE 15. Relative energies (kcal/mole) of the tautomers of protonated formamide.

reported *PA* values for acetaldehyde and formic acid and it is very hard to choose among them. However, if we accept −175 kcal/mole for HCOOH and −185 kcal/mole for $HCOOCH_3$ as recommended by Mills and coworkers[97] then we may use these values to bracket the *PA* of $HCONH_2$.

If we interpolate linearly we obtain a *PA* value for $HCONH_2$ to be −180 kcal/mole, while linear extrapolation to HCOF gives a *PA* value of −170 kcal/mole. However, there is no guarantee that the functional dependence of the *PA* on the atomic number (Z) of the first atom in the substituent X in the formyl derivative is



linear. However, even if the functional dependence is not linear, as Figure 16 suggests, we can be sure that the *PA* value of $HCONH_2$ is in between the *PA* values of $HCOCH_3$ and HCOOH.

As far as different directions of attack are concerned the σ_O (i.e. the in-plane oxygen) protonation resulted in a greater energy lowering than either the π_O or π_N protonation[104]. This finding was in agreement with earlier work involving electrostatic potential contours[105]. Similar findings were reported[106] for the interaction of formamide and other cations such as Na^+ and K^+.

Theoretical studies of protonation of other acid derivatives such as esters and anhydrides have not been made. However, an experimental study on the *PA* values

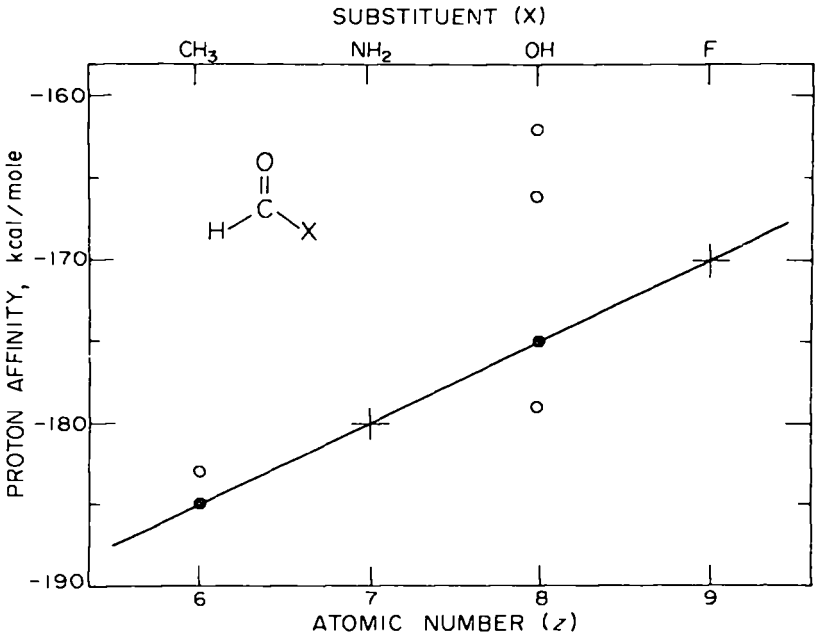


FIGURE 16. Experimental proton affinities of acetaldehyde and formic acid. The most reliable data (see text) are shown as solid circles, and may be used to predict the *PA* of formamide and formyl fluoride.

TABLE 15. Experimental proton affinity values (kcal/mole) for various esters RCOOR' as function of R and R'

R	R'			
	H[a]—	CH_3—	CH_3CH_2—	$CH_3CH_2CH_2$—
H—	−175	−188	−198	−198
CH_3—	−188	−202	−205	−207
CH_3CH_2—	−190	−205	–	–

[a]This column contains *PA* values of carboxylic acids.

of a selected set of small esters, RCOOR', revealed[97] a moderate dependence on the size of the two alkyl groups R and R' as can be seen from Table 15.

B. Hydrogen Bonding, Dimerization and Solvation

The gas-phase protonation discussed earlier is a process in which a bare proton is attached to a base B:

$$B: + H^+ \xrightarrow{PA} B{-}H^+$$

The energy liberated ($\Delta E < 0$), the proton affinity ($PA \equiv \Delta E < 0$), is relatively large because one actually forms a new chemical bond in a protonation process.

In solution, however, there is no bare proton, since it is always attached to a base. Consequently protonation in solution is always a proton-transfer reaction involving transfer from one base to another:

$$B: + H{-}A^+ \xrightarrow{\Delta E_{pt}} B{-}H^+ + :A$$

The energy change associated with this proton transfer (ΔE_{pt}) may be either negative or positive depending on the relative basicity of A and B. However the energy change in this proton transfer (ΔE_{pt}) is not the same as the difference in proton affinity:

$$\Delta E_{pt} \neq \Delta PA$$

This is due to the fact that hydrogen bonding takes place before the proton transfer:

$$B: + HA^+ \overset{\Delta E_{hb}}{\rightleftharpoons} [B: \ldots . H{-}A]^+ \overset{\Delta E_{pt}}{\rightleftharpoons} [B{-}H \ldots . :A]^+ \overset{\Delta E_{hb'}}{\rightleftharpoons} B{-}H^+ + A$$

The energy lowering due to hydrogen bonding (ΔE_{hb} and $\Delta E_{hb'}$) is a measure of the strength of hydrogen bonding but of course it has a different value for the two different bases:

$$\Delta E_{hb} \neq \Delta E_{hb'}$$

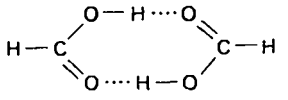
However, with these quantities at hand one may build up a thermochemical cycle that interrelates all these values:

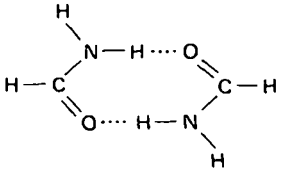
$$PA(B) - PA(A) = \Delta PA = |\Delta E_{pt}| + \{|\Delta E_{hb'}| - |\Delta E_{hb}|\} \tag{57}$$

This thermochemical relationship is illustrated by Figure 17.

Figure 17 also illustrates the kinetic aspect of the proton transfer in the form of a double-well potential. Of course if A and B are identical the double-well potential must be symmetrical but for $A \neq B$ a more general non-symmetrical double-well potential must prevail.

In the case of some acid derivatives, such as esters, hydrogen bonding may occur if, and only if, the other component is a proton donor. However, carboxylic acids and amides may act as proton donors as well. Since acids and amides have this amphoteric character they may form hydrogen-bonded dimers:





Formic acid dimer was studied by a number of authors[51,107-109].

Ady and Brickmann[51] investigated the problem in depth. They found that the energy of dimerization, which is a measure of the hydrogen-bond strength (E_{hb}),

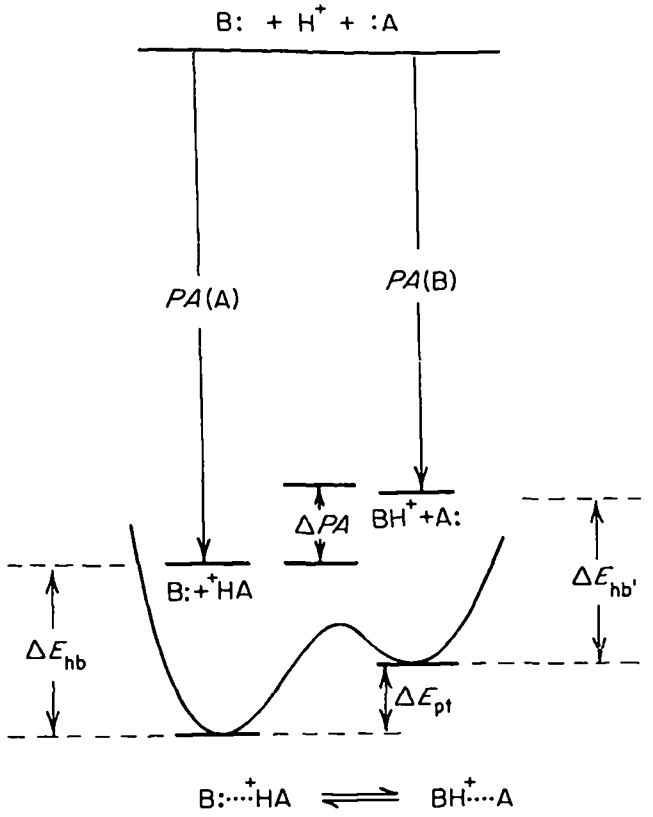
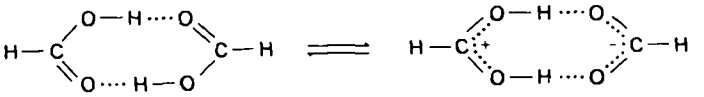


FIGURE 17. The relationship of the proton affinities (PA) to the hydrogen bond strengths (ΔE_{hb}, $\Delta E_{hb'}$) and the energy of proton transfer (ΔE_{pt}).

was −13.8 kcal/mole, which compared well with the experimentally determined value (−14.2 kcal/mole)[110].

As far as the proton transfer is concerned we may distinguish two processes: the single proton transfer and the double proton transfer. In the single proton transfer we generate an ion pair:

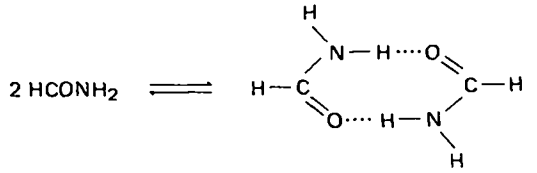


and clearly such a charge separation is an unfavourable process from energetic considerations. The double proton transfer however will regenerate the original situation:

Consequently this reaction is neither hindered or favoured by thermodynamic energetics (i.e. $E_{pt} = 0$). Only the barrier height of this interconversion will determine the feasibility of this double proton transfer. Ady and Brickmann[51] calculated this barrier height to be 59 kcal/mole. However, as was shown (cf. Figures 3 and 4 of Reference 51), the calculated barrier to proton transfer was very sensitive to the sophistication of the calculation made, and it decreased significantly (from 59 to 44 kcal/mole) when the C–O bond lengths were allowed to vary (instead of being fixed) as the two hydrogens migrated.

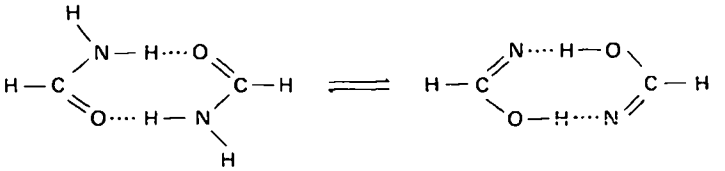
Morokuma and coworkers[109] also studied the double proton transfer not only for the ground state but for several of the π^*-type excited states, but with the C–O bond lengths fixed. They found that the potential curves for the excited states are qualitatively quite similar to that of the ground state, but with increased barrier height.

As far as the heat of dimerization of formamide is concerned:

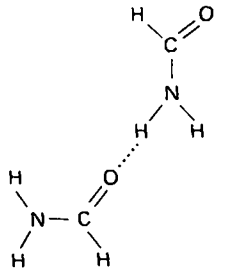


Pullman and coworkers[107] computed an exothermic value of −14 kcal/mole of dimer which is in excellent agreement with the experimental value of −7 kcal/mole per hydrogen bond[111].

Janoschek[81] studied the vibrational spectra of formamide dimer and found the motions of the two hydrogen atoms were coupled. However, the completion of double proton transfer along the mode of coupled vibration is an energetically unfeasible process because it leads to formation of two moles of the unstable tautomeric form of formamide.



There is however a chance for non-cyclic dimerization. One of the geometrical arrangements studied by Dreyfus and Pullman[112] was as follows:



They found a Morse-type of potential for this single hydrogen-bonded dimer with a depth (i.e. ΔE_{hb}) of 7.94 kcal/mole occurring at an O . . . . N distance of 2.85 Å, as

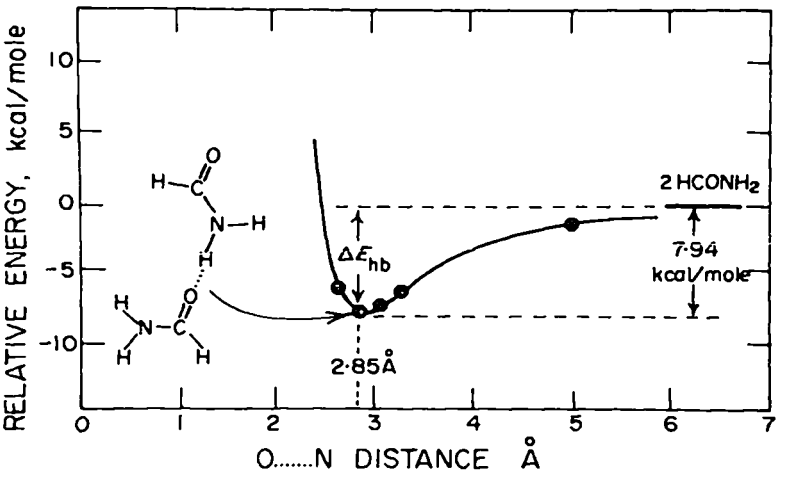
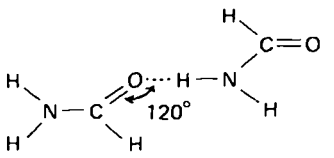


FIGURE 18. Potential function for the linear hydrogen bonding of two formamide molecules. The optimum O . . . N distance is 2·85 Å.

shown in Figure 18. This structure was relatively insensitive to geometrical variation. For example, rotation along the C=O . . . . H—N axis that interchanges the *s-cis* NH_2 and CHO structure with the *s-trans* arrangement requires only about 0.03 kcal/mole[113] while bending the hydrogen-bonded H—N unit away from the

C=O axis lowers the energy about 1.5 kcal/mole[112] on going from an *sp* (180°) to an sp^2 (120°) arrangement



This result was confirmed by Johansson and Kollman[114] who calculated the heat of dimerization to be −9.4 kcal/mole at an O . . . N separation of 2.80 Å, also for the bent (sp^2) geometry.

Needless to say this great interest in the hydrogen bonding of formamide stems from the importance of hydrogen bonding in peptides and proteins[115]. Formamide, the simplest peptide bond containing molecule, serves as a model.

On turning to solvation (hydration in aqueous solution) we realize that the solvent molecules near the peptide unit (i.e. in the primary solvation shell) must be specifically engaged in hydrogen bonding. For this reason there have been five investigations[72,114,116-118] of amide–water hydrogen bonding. The findings summarized in Table 16 for the configurations[116] shown in Figure 19 indicate that hydrogen bonding between an amide and water, whether the water acts as a proton

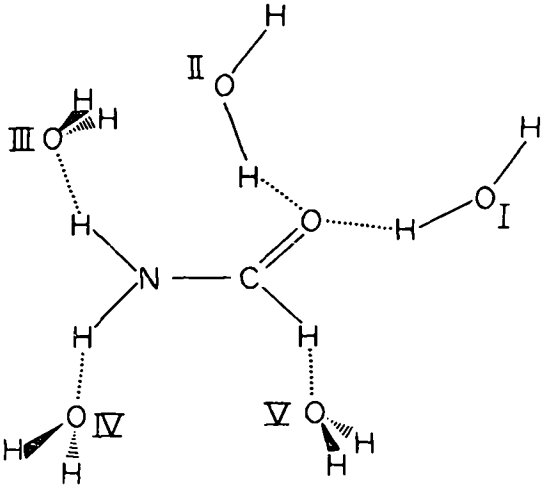


FIGURE 19. Sites of formamide hydration. Sites VI and VII (not shown) have the water molecules hydrogen bonding through the π system above (or below) the N and O atoms respectively.

TABLE 16. A comparison of the energy of hydration for the various sites of formamide shown in Figure 19

	ΔE_{hb}(kcal/mole)		
Dimer	Ref. 116	Ref. 72	Ref. 118
I	−9.4	−6.3	−5.1
II	−9.2	−6.7	−6.4
III	−8.2	−7.6	−7.2
IV	−7.2	−7.3	−6.4
V	−3.0	–	–
VI	−1.8	*a*	–
VII	–	−2.0	–

[a]No stable dimer was found for π-type hydrogen bonding near the N atom.

donor or acceptor, is not fundamentally different, energetically or geometrically, from hydrogen bonding between two amides.

The four most favoured sites (I to IV) have the water O atom in the plane of the formamide molecule, complexing either the carbonyl O or the amide H atoms. Hydrogen bonding to the formyl H atom (site V), and through the π system (sites VI and VII) is clearly disfavoured[72,116,118]. The results from Table 16, all using the same basis set, show the effect of even partial geometry optimization (References 72 and 118) instead of choosing rigid but reasonable geometries (Reference 116).

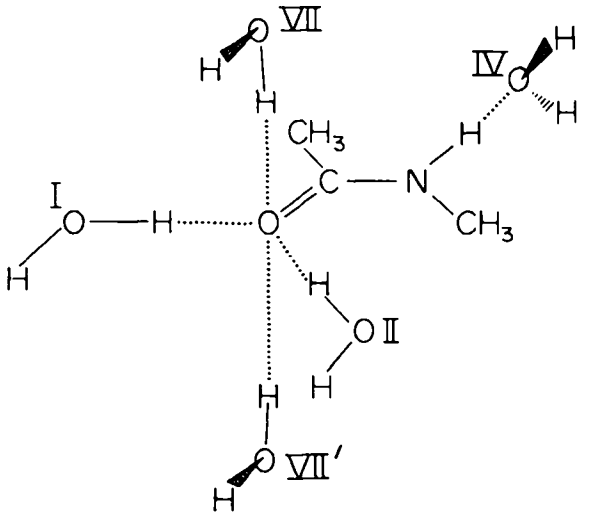


FIGURE 20. Hydration sites for *N*-methylacetamide, using the same notation as Figure 19.

In addition, Kollman and coworkers[72] discussed the basis-set dependence of their results for formamide–water dimers. They also studied several 1:2 formamide:water trimers, with the water molecules occupying two of the sites (Figure 19), or bonding to a water molecule already present (in effect, belonging to the second solvation shell). The stabilization energies varied from −10.2 to −15.8 kcal/mole if neither water was hydrogen bonded to the π system. Del Bene[118] obtained similar results for the trimers studied.

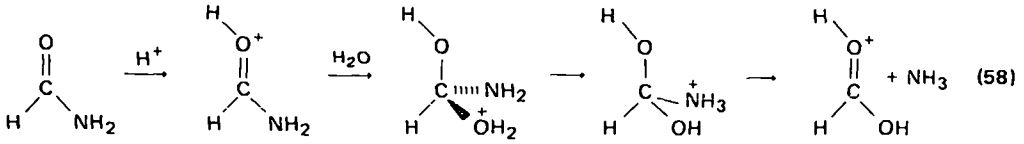
Pullman and coworkers[119] showed that there are three sites of hydrogen bonding in a peptite unit as mimicked by *N*-methylformamide (sites I, II and IV of Figure 20). More recently Scheiner and Kern[120] reinvestigated the nature of the primary solvation shell of a peptide bond using *N*-methylacetamide as the model. They found that there are five sites involved, one has water bonded to the amide group while the remaining four have the waters coordinated about the carbonyl oxygen. Of these four sites two were in the plane as discussed previously (sites I and II of Figure 20) and the remaining two were situated above and below the plane (sites VII and VII′) as shown in Figure 20.

The stabilizations ranged from −11.7 kcal/mole (site IV) through −6.9 and −6.4 kcal/mole (sites I and II respectively) to −1.2 kcal/mole if both sites VII and VII′ were occupied, which again confirms the weakness of the π-type hydrogen bonds. They also found that having all five sites occupied was actually 1.5 kcal/mole less stable than just filling I, II and IV. Complexes of *N*-methylacetamide with other proton donors and acceptors were also studied.

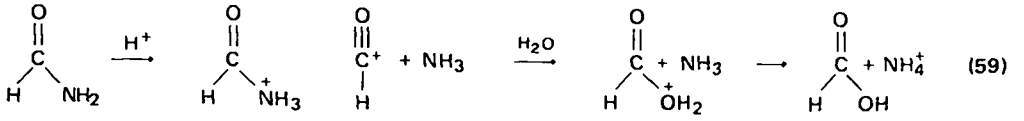
C. Hydrolysis of Amides and Esters

There are a number of reactions that involve nucleophilic addition to the carbonyl group of an acid derivative with or without prior protonation. Examples include esterification, aminolysis, alcoholysis and similar reactions. However, only hydrolysis of amides and esters have been subjected to *ab initio* theoretical study.

Of the two mechanistic schemes of acid-catalysed hydrolysis of amides (equations 58 and 59) only that shown in equation (59) has been investigated[121]. Figure 21 shows the thermodynamic aspect of the energy profile. The acylium ion intermediate of reaction (59) was also studied by Veillard and coworkers[122].

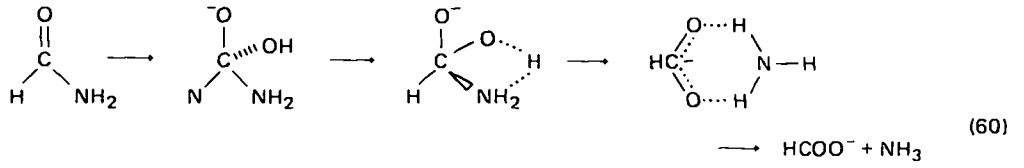


(58)



(59)

As far as the base-catalysed hydrolysis of amides is concerned, Alagona, Scrocco and Tomassi[64] published the thermodynamic aspects of the reaction profile shown in Figure 22 which corresponds to the mechanism shown in equation (60).



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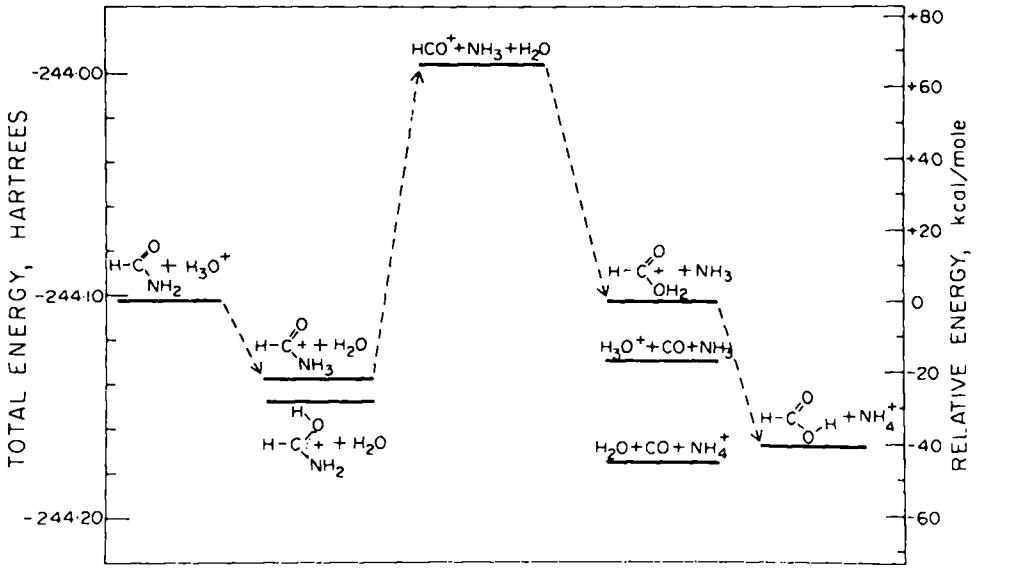


FIGURE 21. Computed reaction profile for the $A_{Ac}1$ hydrolysis mechanism for formamide. Reproduced with permission from A. C. Hopkinson and I. G. Csizmadia, *Theoret. Chim. Acta.*, 31, 83 (1973).

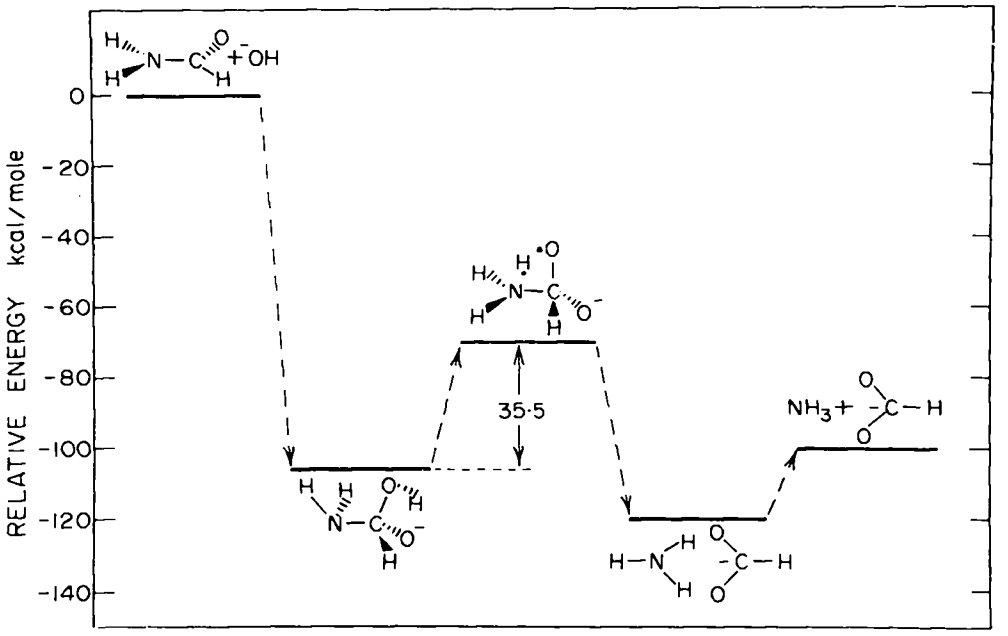
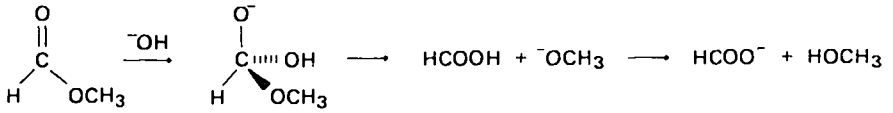


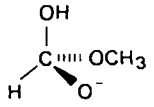
FIGURE 22. Computed reaction profile for the attack of OH^- on formamide. Reproduced with permission from G. Alagona, E. Scrocco and J. Tomasi, *J. Amer. Chem. Soc.*, 97, 6976 (1975).

An *ab initio* study on the base-catalysed hydrolysis of methyl formate has recently been reported[1 2 3] involving the mechanism shown in equation (61). Most



(61)

of the work has focused on the stereochemistry of the first intermediate (**15**). A preliminary study has indicated that the rotation about the C–OH bond (θ_{OH}) has



(15)

a one-fold periodicity with two distinctly different minima while one finds three different minima along the C–OCH_3 rotation (θ_{OCH_3}). This leads to an energy surface (equation 62) with $2 \times 3 = 6$ minima. The six stable conformations associated with the six minima are shown in Figure 23.

$$E = E(\theta_{OH}, \theta_{OCH_3}) \tag{62}$$

The predicted topology of the energy surface is given in Figure 24. The expected three lower minima A, B, C, and the three higher minima a, b, c, are marked in both

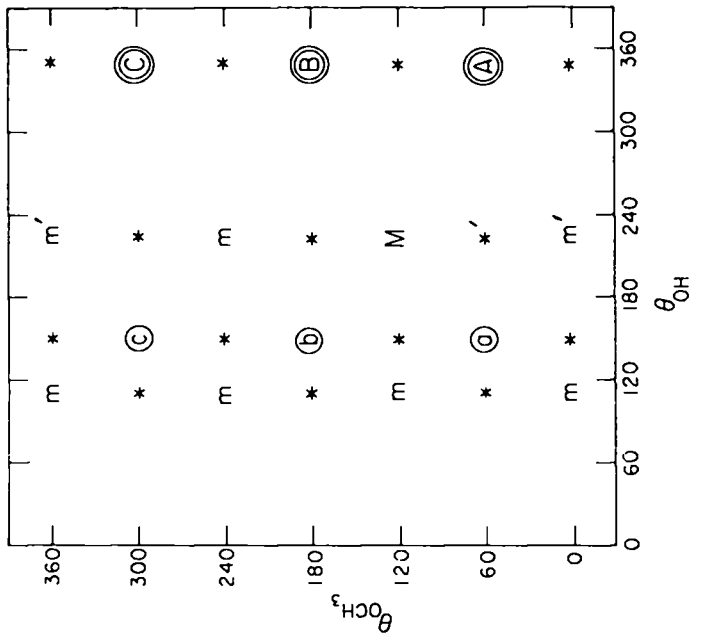


FIGURE 24. Predicted topology of the conformational energy surface for the tetrahedral intermediate. A, B and C are low minima, while a, b and c are high minima (the conformations are shown in Figure 23). The *s are the saddle points, m are low maxima and M is the high maximum. Reproduced with permission from M. H. Lien, A. C. Hopkinson, M. R. Peterson, K. Yates and I. G. Csizmadia, *Progr. Theoret. Org. Chem.*, **2**, 162 (1977).

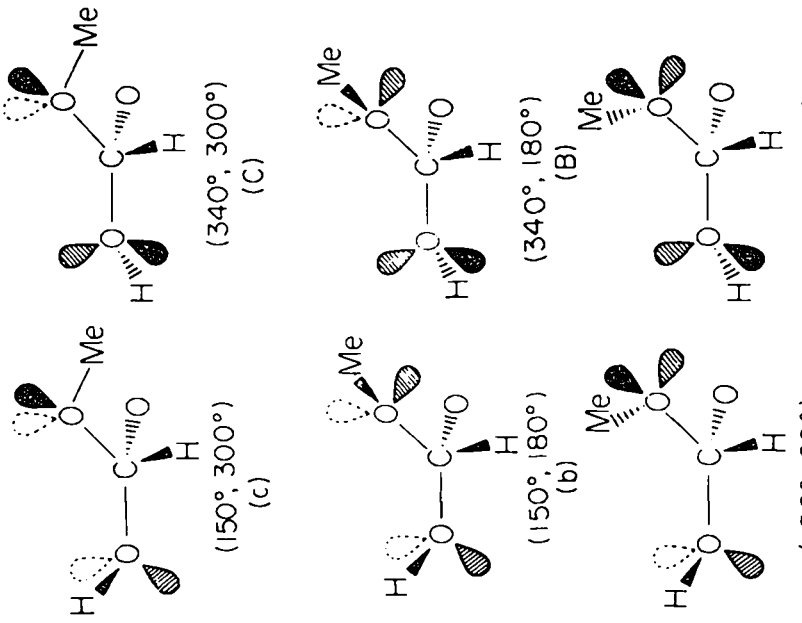


FIGURE 23. Expected stable conformations of the tetrahedral intermediate in the base-catalysed hydrolysis of methyl formate. Reproduced with permission from M. H. Lien, A. C. Hopkinson, M. R. Peterson, K. Yates and I. G. Csizmadia, *Progr. Theoret. Org. Chem.*, **2**, 162 (1977).

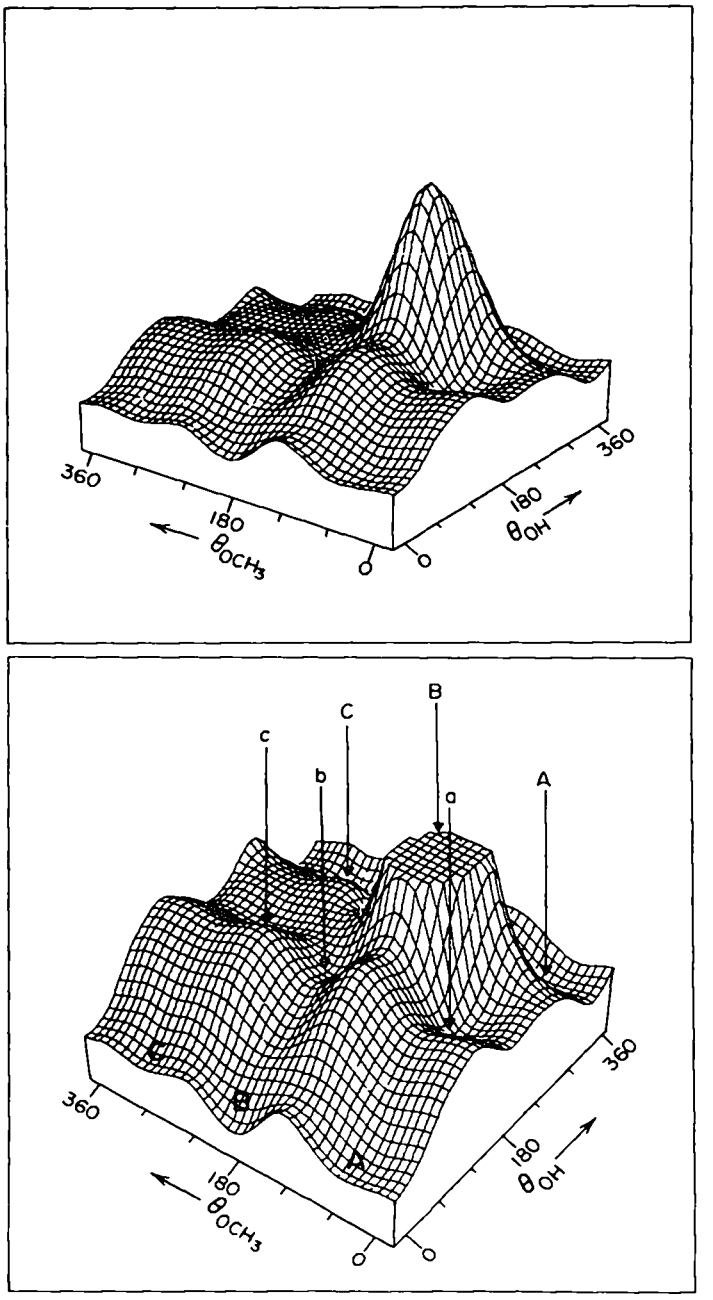


FIGURE 25. Pseudo-three-dimensional representation of the conformational energy surface for the tetrahedral intermediate. The minima are shown in the lower projection. Reproduced with permission from M. H. Lien, A. C. Hopkinson, M. R. Peterson, K. Yates and I. G. Csizmadia, *Progr. Theoret. Org. Chem.*, 2, 162 (1977).

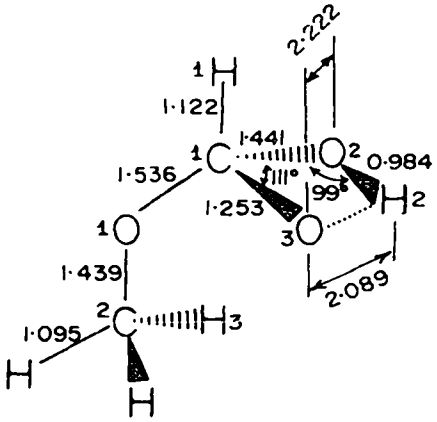


FIGURE 26. Optimum STO-3G geometry for conformation B (see Figures 23 and 24) of the tetrahedral intermediate. Reproduced with permission from M. H. Lien, A. C. Hopkinson, M. R. Peterson, K. Yates and I. G. Csizmadia, *Progr. Theoret. Org. Chem.*, 2, 162 (1977).

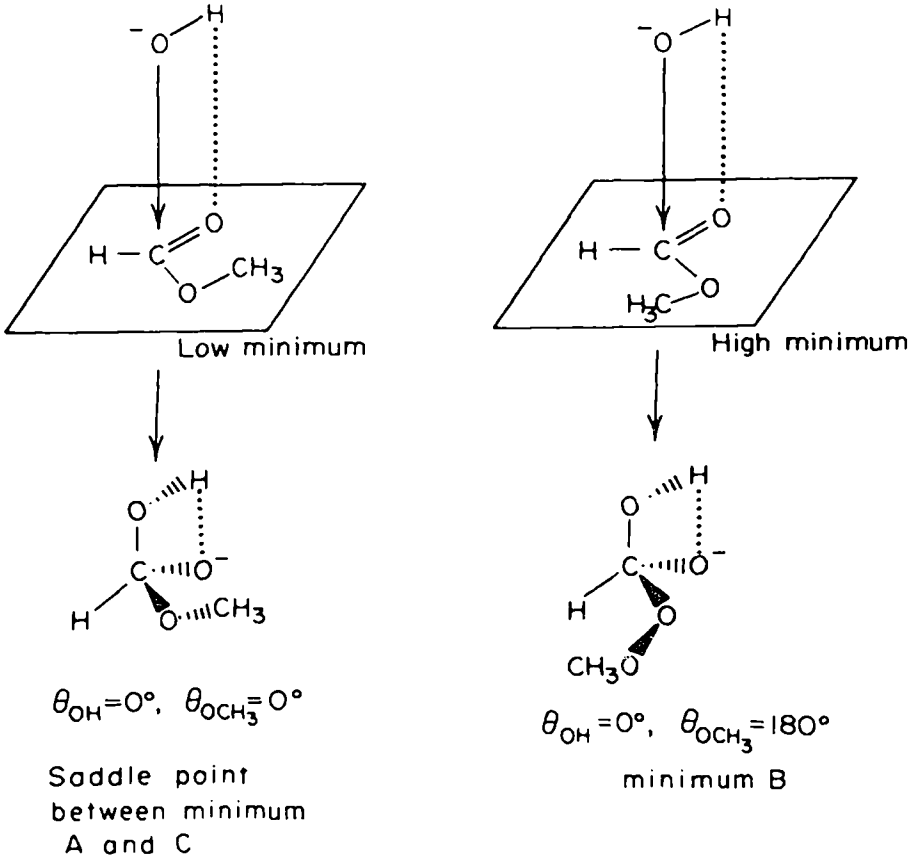
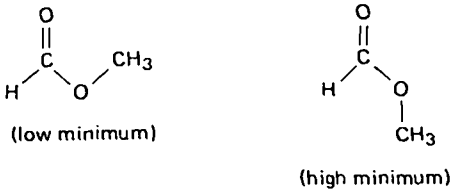


FIGURE 27. Idealized geometry of approach for hydroxide ion on methyl formate and the resulting anions. Reproduced with permission from M. H. Lien, A. C. Hopkinson, M. R. Peterson, K. Yates and I. G. Csizmadia, *Progr. Theoret. Org. Chem.*, 2, 162 (1977).

Figures 23 and 24. The expected topology of the energy surface (Figure 24) also shows the existence of six maxima (m and M), one of which (M) is predicted to be the highest since the OH proton is in close proximity to the CH_3 group. In addition to these the approximate positions of the twelve transition states are shown. The actual computed energy surface is shown in two different enlargements in Figure 25, while Figure 26 shows the optimized geometry of the most stable conformer corresponding to structure B in Figure 23.

As far as the formation of the key intermediate (cf. Figure 26) is concerned we may consider the two stable conformations of methyl formate:



Assuming that the OH^- ion attacks the carbonyl group from a direction perpendicular to the plane formed by the –COO– atoms we may predict that the most

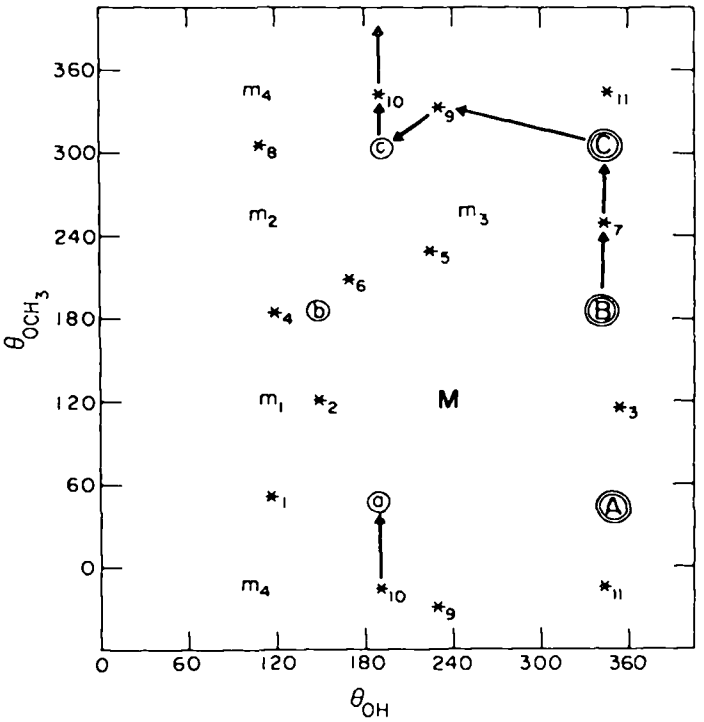


FIGURE 28. Computed topology of the conformational energy surface for the tetrahedral intermediate (the symbols are as defined in Figure 24). Note that *' and m' are not found on this surface. The least-energy path for the reaction B →a is marked by arrows. Reproduced with permission from M. H. Lien, A. C. Hopkinson, M. R. Peterson, K. Yates and I. G. Csizmadia, *Progr. Theoret. Org. Chem.*, 2, 162 (1977).

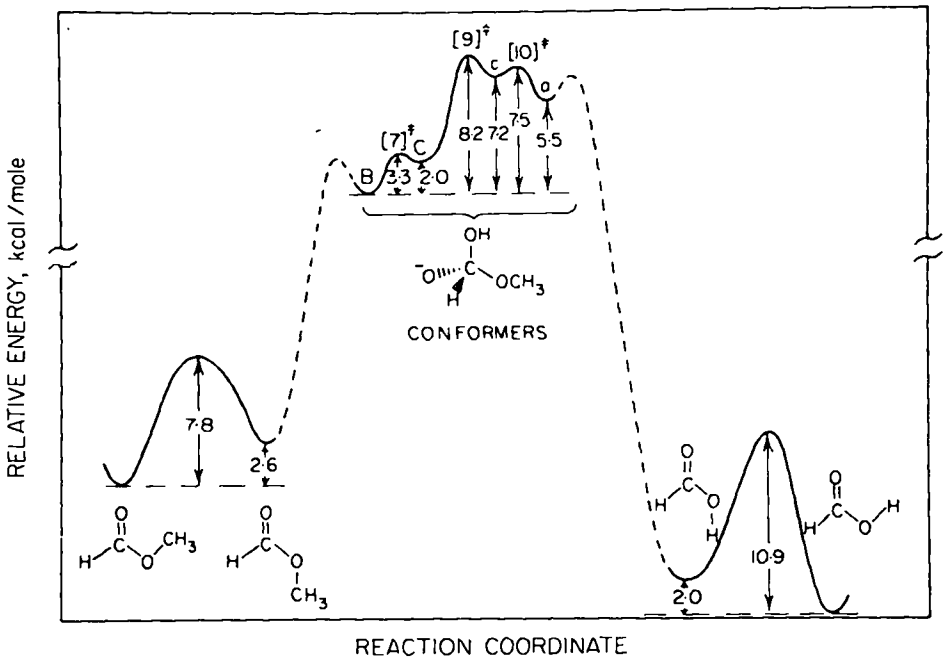


FIGURE 29. Energy profile for the hydrolysis of methyl formate assuming the Deslongchamps model for the intermediate. The conformational portions of the profile are drawn with solid lines and are the result of *ab initio* MO calculations and experimental observations.

stable conformation (low minimum) of $HCOOCH_3$ yields the key intermediate at a saddle point between A and C (cf. Figure 24) while the less stable conformation (high minimum) of $HCOOCH_3$ yields the key intermediate in conformation B (cf. Figures 23 and 24). This conclusion is summarized in Figure 27.

If one assumes that the Deslongchamps model[124] which claims that the tetrahedral intermediate (cf. Figure 26) is most labile, i.e. most likely to decompose, from a conformation in which the maximum number of lone pairs are antiperiplanar to the bond which undergoes cleavage, then clearly the decomposition must occur from conformation a even though it is formed in conformation B. The change of conformation (B → a) must occur not only by avoiding the high maximum M (cf. Figures 24 and 25) but in fact along the least energy path. The computed surface would suggest the following process:

$$B \rightleftarrows C \rightleftarrows c \rightleftarrows a$$

and the actual path including the lowest transition states is shown in Figure 28. The energetic aspect of this conformation change in the reactive intermediate is compared in Figure 29 with the energy changes of the reactant and product.

V. CONCLUSION

In conclusion it is fair to say that the Hartree–Fock theory as formulated for the closed- and open-shell systems is successful in studying both physical and chemical properties of carboxylic acids and their derivatives.

However, one must be wary of the correlation problem that is outside the scope of the Hartree–Fock theory. This, however, is not expected to pose difficulties as long as the pairing scheme of the electrons is not altered in the process investigated. Thus only excitation , ionization and homolytic dissociation demand more sophisticated treatment than the Hartree–Fock theory.

The present state of the art indicates that organic compounds as complex as carboxylic acids and their derivatives may be treated successfully within the framework of quantum chemistry. Consequently it may be hoped that theory and experiment will be practised on equal footing in the foreseeable future.

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Supplement B The Chemistry of Acid Derivatives
Edited by Saul Patai

CHAPTER 2

Thermochemistry of acid derivatives

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'And what is good, Phaedrus,
And what is not good –
Need we ask anyone to tell us these things?'

ROBERT M. PIRSIG

I. INTRODUCTION

This review is concerned with the standard molar heat of formation at 298.15 K of pure organic acids, esters, amides and acyl halides in the gas, liquid and solid state. Although the symbol recommended by IUPAC[1] for the standard molar heat of formation at 298.15 K is $\Delta_f H_m{}^{\theta}$ (chemical formula, state, 298.15 K), I have abbreviated it as $\Delta H_f{}^0$ (chemical formula, state) and have used g, l and c to denote the gas, liquid and crystal (or solid) states.

I have given a lot of thought to the problem of units. IUPAC[1] have recommended that the unit be kJ/mol. Unfortunately almost all of the papers that I have reviewed use kcal/mol, where 1 cal = 4.184 kJ (Reference 2). Furthermore I still think in calories rather than joule. At first I was tempted to use a dimensionless heat of formation, dim.$\Delta H_f{}^0$, defined by dim.$\Delta H_f{}^0 = \Delta H_f{}^0/RT$, where R is the gas constant = 1.987 cal/(mole K) = 8.314 J/(mole K) (Reference 3), and $T = 1$ K. However, Benson[4] pointed out that this was really a third unit and would probably be

unacceptable to the reader. As my previous practice[5] of giving the values in both units was time-consuming, I finally decided to go with the majority and use kcal/mol.

1969 saw the publication of three important works on the heats of formation of acid derivatives. Cox and Pilcher[6] (CP) initially reviewed and gave valuable details on the experimental data. Stull, Westrum and Sinke[7] cover much the same ground but in less detail. Benson and coworkers[8] have reviewed some of the published data for acids, esters and amides (omitting acyl halides) and have compared the experimental results with those estimated by group additivity[9]. In 1973, Eigenmann, Golden and Benson[10] (EGB) revised the comparison between experimental and estimated values for acids and esters using the more thorough literature search of CP and of Stull, Westrum and Sinke. For the purposes of this review I have searched IUPAC's annual *Bulletin of Thermochemistry and Thermodynamics*[11] from 1975 (No. 18) to 1973 (No. 16) for data on acids and esters, and to 1970 (No. 13) for data on amides and acyl chlorides. I have also searched the *Thermochimica Acta* from 1976 (Vol. 17) to 1975 (Vol. 13) (except § 3 of vol. 16, which was unavailable) and the *Journal of Chemical Thermodynamics* for 1976 (Vol. 8) and 1975 (Vol. 7).

II. ACIDS

A. Aliphatic and Alicyclic Acids

Stridh[12] has measured the ΔH_f^0 (= −133.7 ± 0.5 kcal/mol) for 2-ethyl hexanoic acid (g). From other groups[10] I have estimated it to be −133.3 kcal/mol in excellent agreement with the experimental value.

Kolesov, Slavutskaya and Papina[13] (KSP) have measured ΔH_f^0(CF_3COOH, l) = −253.4 ± 0.4 kcal/mol in good agreement with an earlier value[6] of −255.4 ± 0.8 kcal/mol. KSP also report ΔH_f^0 (CF_3COOH, g) = −244.2 ± 0.2 kcal/mol. In a later paper, Kolesov, Slavutskaya and Ditzat'eva[14] (KSD) have reported that the measured value for ΔH_f^0 (CF_3COOH, g) differs by 14.3 kcal/mol from a value that they estimated by group additivity. I do not understand how KSD were able to estimate ΔH_f^0 (CF_3COOH) by group additivity. I have tried to repeat the estimation and have found that there is a missing group namely (C—CO,F_3).

Colomina, Roux and Turrion[15] have found that ΔH_f^0(1-naphthylacetic acid, c) = −85.85 ± 0.42 kcal/mol whereas the 2-isomer is 3.05 kcal/mol more stable. They attribute the difference to steric effects, which is reasonable, especially as the same authors have previously shown[16] that 1- and 2-naphthols which have a much smaller hydroxyl group differ by only 0.04 kcal/mol. Mikina, Oleinik, Aleksandrov and Khrustaleva[17] have measured ΔH_f^0 (succinic acid, g) = −224.6 kcal/mol. This is in excellent agreement with the value of −224.75 ± 0.13 kcal/mol recommended by Vanderzee, Mansson and Sunner[18], who reviewed 18 experimental studies and concluded that 'succinic acid, properly purified and dried, is an excellent test substance for combustion calorimetry'. Arshadi[19] has measured the heat of sublimation of succinic acid to be 28.9 ± 0.4 kcal/mol from 333 to 387 K, in good agreement with the value of 28.1 ± 0.8 kcal/mol at 298 K recommended[6] by CP. I am guessing that the heat capacity correction would make the agreement even better.

EGB[10] draw attention to the poor agreement (off by 6.1 kcal/mol) between measured and estimated values of ΔH_f^0 [sebacic acid (decanedioic acid), g]. EGB point out that the ΔH_f^0 was obtained by combustion in 1926. This experiment

should be repeated. EGB also mention the differences (6.8 and 8.9 kcal/mol) between measured and estimated values of ΔH_f^0(maleic acid, g) and ΔH_f^0 (fumaric acid, g).

Steele, Carson, Laye and Rosser[20] have measured ΔH_f^0 (adamantane-1-carboxylic acid, c) = -153.70 ± 0.90; that for the 2-isomer = -149.90 ± 0.90 kcal/mol. They compare these results with other heats of isomerization for adamantane systems and support Engler, Blanchard and Schleyer's[21] conclusion that the axial substituent strains in adamantanes should be enhanced over those in the more flexible cyclohexane systems.

B. Aromatic Acids

EGB[10] have found that the difference between measured and estimated values of ΔH_f^0 (benzoic acid, g) is a surpisingly large 5.1 kcal/mol. This difference may be due to an error in the measured heat of formation of solid benzoic acid, or its heat of sublimation as suggested by EGB or an error in the group value due to errors in the heats of formation of esters as suggested by Benson[4].

Mikina, Oleinik, Aleksandrov and Krustaleva[17] have measured ΔH_f^0 (benzoic acid, c) = -92.20 kcal/mol in good agreement with the value of -91.99 ± 0.05 kcal/mol recommended by CP, so error in the heat of formation of solid benzoic acid is not likely to be the cause of the discrepancy between estimated and observed values.

As regards the heat of sublimation of benzoic acid, Malaspina, Gigli and Bardi[22] have reviewed seven measured values between 20.32 and 22.58 kcal/mol. Other recent measurements are 22.2 ± 0.5 kcal/mol (Knudsen method) by Arshadi[19], 21.1 kcal/mol (free molecular evaporation) by McEachern and Sandoval[23] and 21.05 ± 0.05 kcal/mol by Kruif and Oonk[24]. Earlier, CP recommended 21.85 ± 0.1 kcal/mol. All of the measured values fall in the range of 21.4 ± 1.2 kcal/mol so it is very unlikely that the discrepancy between estimated and measured values for ΔH_f^0 (benzoic acid, g) are due to errors in the measured heat of formation.

Some recent measurements of the heat of formation of benzoic acid and some substituted benzoic acids[19,25-30] are in Table 1. For each compound a value of the sum of the groups $(C_B{-}CO) + (CO{-}C_B,O)$ has been derived by substracting the rest of the groups[8,9] from the measured ΔH_f^0 (acid, g). The data show that the values for the sum of these groups range from -27.6 to -40.2 kcal/mol. EGB recommend that $(C_B{-}CO) = 3.7$ and $(CO{-}C_B,O) = -36.6$ kcal/mol, giving -32.9 kcal/mol as the sum of the two groups. Therefore the difference between observed and estimated values for the compounds in Table 1 will range from $-27.6 + 32.9 = 5.3$ to $-40.2 + 32.9 = -7.3$ kcal/mol. No matter what values are selected for the groups $(C_B{-}CO)$ and $(CO{-}C_B,O)$ it is clear that the maximum difference between observed and estimated values cannot be less than $1/2(5.3 + 7.3) = 6.3$ kcal/mol. I do not know why this maximum difference is so large.

Colomina, Roux and Turrion[31] have measured ΔH_f^0(1-naphthoic acid, g) = -53.3 ± 0.3 and ΔH_f^0(2-naphthoic acid, g) = -55.6 ± 0.4 kcal/mol. They account for the difference in heats of formation in terms of the molecular structures[32] of the acids. The 2-naphthoic acid is planar, whereas in 1-naphthoic acid, the carboxyl group is 11° out of the plane of the naphthalene. I have estimated that ΔH_f^0(2-naphthoic acid, g) = -58.3 kcal/mol from ΔH_f^0 (naphthalene) and the appropriate groups[6,10]. The difference between observed and estimated values is 2.7 kcal/mol which is reasonable.

TABLE 1. Recently-measured heats of formation of organic acids at 298.15 K in kcal/mol

Compound	ΔH_f^0(c)	ΔH_{subl}	ΔH_f^0(g)	Reference
Benzoic acid PhCOOH	−92.1 ± 0.1	21.4 ± 1.2	−69.7 ± 1.2	See text
o-Chlorobenzoic acid	−95.3 ± 2.0	19.0 ± 0.8	−76.3 ± 2.2	6
ClC_6H_4COOH	−96.7 ± 0.2			25
	−96.7 ± 0.2	19.0 ± 0.8	−77.7 ± 0.8	Selected
m-Chlorobenzoic acid	−101.2 ± 2.0	19.6 ± 0.8	−81.6 ± 2.2	6
ClC_6H_4COOH	−101.4 ± 2.0			25
	−101.4 ± 2.0	19.6 ± 0.8	−81.6 ± 2.2	Selected
p-Chlorobenzoic acid	−102.2 ± 0.4	21.0 ± 0.8	−81.2 ± 0.9	6
ClC_6H_4COOH	−102.8 ± 0.3			26
	−102.8 ± 0.8			27
	−102.0 ± 0.3			28
	−102.4 ± 0.4	21.0 ± 0.8	−81.4 ± 0.9	Selected
3,5-Diethylbenzoic acid $Et_2C_6H_3COOH$	−122.3	24.9	−97.4	29
3,5-Di(*t*-butyl)benzoic acid $(t\text{-Bu})_2C_6H_3COOH$	−149.3	25.9	−123.4	29
2-Hydroxybenzoic acid		23.7 ± 0.5		19
HOC_6H_4COOH	−141.0 ± 0.2	22.7 ± 0.1	−118.3 ± 0.2	6
1,3-Benzenedicarboxylic acid $C_6H_4(COOH)_2$	−191.9 ± 0.6	25.5 ± 0.5	−166.4 ± 0.6	6
1,4-Benzenedicarboxylic acid $C_6H_4(COOH)_2$	−195.0 ± 0.2	23.5 ± 0.6	−171.6 ± 0.7	6
o-Toluic acid $CH_3C_6H_4COOH$			−76.5 ± 0.2	30
m-Toluic acid $CH_3C_6H_4COOH$			−78.8 ± 0.2	30
p-Toluic acid $CH_3C_6H_4COOH$			−79.4 ± 0.3	30
o-Ethylbenzoic acid $C_2H_5C_6H_4COOH$			−81.4 ± 0.4	30
m-Ethylbenzoic acid $C_2H_5C_6H_4COOH$			−82.9 ± 0.4	30
p-Ethylbenzoic acid $C_2H_5C_6H_4COOH$			−86.8 ± 0.4	30

Sabbah, Chastel and Laffitte[33] have measured the heat of sublimation of 2-, 3- and 4-aminobenzoic acids to be 25.1 ± 0.2, 30.6 ± 0.8 and 27.7 ± 0.9 kcal/mol and have accounted for the values on structural grounds.

III. ESTERS

A. Esters Containing only C, H and O

Connett, Counsell and Lee[34] have measured the heats of vaporization of methyl, ethyl and *n*-propyl acetates to be 7.7, 8.5 and 9.4 kcal/mol. The latter two values are in excellent agreement with previous work[35].

Mansson[36] has found ΔH_f^0 (ethyl propionate, g) = −110.8 ± 0.2 kcal/mol in good agreement with a previously measured [16,10] value of −112.2 ± 0.6 kcal/mol and an estimated[10] value of −111.7 kcal/mol.

The thing that surprises me most about the esters containing only C, H and O concerns triacetin (glycerol triacetate), and diethyl-, di-*n*-butyl- and di-*n*-pentyl phthalates. The differences between estimated and observed values[10] in each case are greater than 8 kcal/mol.

Another unusual result is that Delafontaine, Sabbah and Laffitte[37] report a precision of ±10 kcal/mol in their measurement of ΔH_f^0 (*n*-propyl formate, l) = 115.7 kcal/mol.

Zaikin, Shibanov and Federova[38] report that the heats of formation of *t*-butyl *OO*-methyl peroxyfumarate, *t*-butyl *OO*-methyl peroxysuccinate and *t*-butyl methyl succinate in the liquid phase are −178.5 ± 0.4, −209.9 ± 0.6 and −227.3 ± 0.7 kcal/mol.

Anthoney, Cason, Laye and Yurekli[39] report that the heat of formation of solid dimethyl oxalate is −180.8 ± 0.1 kcal/mol and that of the gaseous ester is 169.5 ± 0.1. The solid-phase value is in excellent agreement with the previously measured value[7] of −179.9 kcal/mol. The gas-phase value agrees less well with a value of −165.0 kcal/mol that I have estimated from group additivity[10].

Colomina, Roux and Turrion[15] have found ΔH_f^0(1-naphthyl acetate, c) = −72.9 ± 0.5 kcal/mol, and that of the 2-isomer = −74.0 ± 0.5 kcal/mol. The greater stability of the 2-isomer is explained on the basis of less steric hindrance.

B. Halogenated Esters

Kolesov, Slavutskaya and Ditzat'eva[14] (KSD) have measured (a) $\Delta H_f^0[(CF_2)_3(COOCH_3)_2, g]$ = −455.9 kcal/mol. Earlier Slavutskaya, Kolesov and Borisov[40] had reported (b) $\Delta H_f^0(C_2F_5COOCH_3, g)$ = −337.5 kcal/mol. KSD have estimated values for (a) and (b) by a method that they call group additivity and have found that the difference between observed and estimated values is greater than 10 kcal/mol in each case. I do not understand their method. I have estimated the heats of formation by group additivity, and found a value for the group $(C-C,CO,F_2)$ = 91.0 kcal/mol, which gives a difference (observed minus estimated) for (a) to be −0.4 kcal/mol and for (b) to be +0.2 kcal/mol.

Finally, I wish to draw attention to a number of values for the heat of formation of halogenated esters (and acids) in Cox and Pilcher[6] which have not been used to derive groups for the purposes of estimation.

IV. AMIDES

In 1969, Walsh and Benson[8] derived group values for estimating heats of formation of amides. They concluded that 'there are no checks whatsoever on the group values for heats of formation among the amides, therefore this table (of observed and estimated data on amides) probably contains the least reliable information of any class of nitrogen-containing compounds listed thus far. However, . . . these data are probably good to better than ±2 kcal/mol'. Table 2 gives data now available on the alkanamides. From the observed data, I have derived the value of the $(N-CO,H_2)$ group as −14.3 compared with Walsh and Benson's −14.9 kcal/mol. The difference between observed and estimated heats of formation is better than 1 kcal/mol in all cases except pentanamide where it is 2.7 kcal/mol. (I excluded pentanamide when deriving the group value.)

Hamilton and Witt[44] have found the heat of formation of the diamide of 1,4-dicarboxybenzene in the gas phase to be −89.8 kcal/mol. From the heat of formation I have derived a value of −40.3 kcal/mol for the new group $(CO-N,C_B)$.

TABLE 2. Observed and estimated heats of formation of organic amides at 298.15 K in kcal/mol

Compound	Obs. ΔH_f^0(g)	Reference	Est. ΔH_f^0(g)	Obs. – est.
Ethanamide	−57.0 ± 0.2	41		
CH_3CONH_2	−57.8	42		
	−57.4 ± 0.4	Selected	−57.2	−0.2
Propanamide	−61.9 ± 0.2	41	−62.2	0.3
$C_2H_5CONH_2$				
Butanamide	−66.7 ± 0.2	41		
$C_3H_7CONH_2$	−66.6 ± 0.4	43		
	−66.7 ± 0.2	Selected	−67.2	0.5
Pentanamide	−69.4 ± 0.3	42	−72.1	2.7
$C_4H_9CONH_2$				
Hexanamide	−78.3 ± 0.3	42		
$C_5H_{11}CONH_2$	−77.5 ± 0.4	43		
	−78.2 ± 0.7	Selected	−77.1	−1.1
Octanamide	−86.7 ± 0.8	42	−87.0	0.3
$C_7H_{13}CONH_2$				

TABLE 3. Observed heats of formation and derived group values for estimating heats of formation of acyl halides at 298.15 K in kcal/mol

Compound	ΔH_f^0(g)	Reference	Group	Group value
Acetyl fluoride	−106.4	6	CO–C, F	−96.3
CH_3COF				
Acetyl chloride	−60.1	47		
CH_3COCl	−58.4	6		
	−60.1	Selected	CO–C, Cl	−50.0
Trichloracetyl chloride	−56.6	6	C–CO, Cl_3	−6.6
CCl_3COCl				
Dichloracetyl chloride	−57.7	6	C–CO, H, Cl_2	−7.7
$CHCl_2COCl$				
Chloroacetyl chloride	−58.7	6	C–CO, H_2, Cl	−8.7
$CH_2ClCOCl$				
Acetyl bromide	−46.8	47		
CH_3COBr	45.6	6		
	−46.8	Selected	CO–C, Br	−36.7
Acetyl iodide	−31.2	47		
CH_3COI	−30.1	6		
	31.2	Selected	CO–C, I	−21.1
Benzoyl chloride	−25.2	48, 6		
	26.1	6		
	−25.7	Selected	CO–C_3, Cl	−45.9
Benzoyl bromide	−11.6	6	CO–C_3, Br	−31.8
PhCOBr				
Benzoyl iodide	2.5	6	CO–C_3, I	−17.7
PhCOI				
Oxalyl chloride	−78.0	6	CO–CO, Cl	−39.0
$(COCl)_2$				

Vasol'eva, Zhil'tsova and Vvedenskii[45] have measured the heat of formation of liquid *N,N*-dimethylformamide and *N,N*-dimethylacetamide as -57.2 ± 0.3 and -66.5 ± 0.4 kcal/mol. The former value is in excellent agreement with a previously measured value[6] of -57.1 kcal/mol. From the heat of formation of gaseous *N,N*-dimethylformamide[6], I have derived the new group value $(N=CO,C_2) = 4.0$ kcal/mol.

Finally, Wadso[42] and Walsh and Benson[8] prefer an estimate of 25 ± 1 kcal/mol rather than the measured[46] value of 19.3 kcal/mol for the heat of vaporization of acetanilide whereas Cox and Pilcher's[6] value for the gas-phase heat of formation is based on the experimental value.

V. ACYL HALIDES

Group values have not previously been derived for the acyl halides. The experimental data are summarized in Table 3. Most of the values are from Cox and Pilcher[6]. Devore and O'Neal's results[47] for acetyl chloride, bromide and iodide, and Hu and Sinke's result[48] for benzoyl chloride are included. Each compound was the sole source for one group so there are no checks. The group values are listed in Table 3.

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER 3

Chiroptical properties of acid derivatives

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I. INTRODUCTION

Carboxylic acids, and their simple derivatives such as esters and amides, absorb at relatively short wavelengths and therefore not even their first low energy absorption band and the associated Cotton effect (CE) could be reached with the early commercial instruments. Not until the beginning of the sixties had the instrumentation been developed to permit chiroptical measurements to be performed to below 200 nm, and thereby into the $n \rightarrow \pi^*$ transition band of carboxylic acids. Before that time, in cases where the study of plain optical rotatory dispersion (ORD) curves was found unsatisfactory, ORD, and to a much smaller extent circular dichroism (CD), investigations were performed on various derivatives with CEs at accessible longer wavelengths. A chronological treatment of the subject should thus start with such ORD work. However, since today ORD has been almost completely replaced by the CD technique (with some exceptions; see for example Section IV.A.2.c), and following the intention of this series to concentrate on the most important recent developments, the main interest of this chapter will be focused on CD investigations representative of the past ten years.

The chiroptical properties of acid derivatives are not well understood, and progress is slow despite hard work. There are mainly two factors responsible for this state of affairs. One is our incomplete knowledge of the electronic properties of the carboxyl group itself and of derivatives such as α-amino and α-hydroxy acids (Section IV.A.1.b). The other is insufficient information about preferred geometries of the molecules in nearly all cases. Exceptions are small ring lactones and lactams, in which the group of interest is locked in a definite position relative to the rest of the molecule. Therefore these compounds are best suited for the evaluation of the CD sign–geometry relationships, and consequently they have received relatively great interest.

Acid derivatives include the amide group, which constitutes one of the most important chromophores because of its presence in peptides and proteins. Certain structures of these compounds represent other examples of known molecular

geometries. Although still incomplete, much of our present knowledge of the chiroptical properties of the carboxyl and amide chromophores has been obtained thanks to the great interest devoted to the fundamental components amino acids and amides by experimentalists as well as theoreticians. Some of the research in this field will be described below. However, the chiroptical properties of the polyamino acid macromolecules cannot be considered in detail within the limits of this chapter. Usually these compounds are not included under acid derivatives, but form special sections in reviews on ORD and CD. Nevertheless their chiroptical properties as acid derivatives are most interesting.

For a more detailed presentation of subjects which have not been considered here at all or only very briefly, for leading references in these cases and to early work in particular, and for basic principles and fundamental aspects of ORD and CD, the reader is referred to the many excellent general books on the subject. In addition to those written by Crabbé[1-3] and by Velluz, Legrand and Grosjean[4] there are two others which include proceedings of a NATO Summer School held at Bonn in 1965[5] and of a NATO Advanced Study Institute held at Tirrenia (Pisa) in 1971[6], where lectures were presented by several recognized authorities in the field. Reference is often made to these proceedings in the following sections. A more recent paper by Schellman[7], in which the theory of circular dichroism is considered, may also be recommended.

II. ELECTRONIC PROPERTIES OF THE CARBOXYL GROUP

The electronic properties of the carboxyl group have already been given an excellent review by Simonetta and Carrà in the main volume[8]. However, for the present case it may be desirable to recall and draw special attention to some features in the electronic spectra of carboxylic acids and their derivatives. On comparing ORD or CD data it is of utmost importance to select the Cotton effects (CEs) associated with related electronic transitions. As will be evident below, by considering solely the CD spectra it is for example very easy to confuse the $\pi \rightarrow \pi^*$ CE of a tertiary amide with that originating from an $n \rightarrow \pi^*$ transition of a carboxylic acid. Comparison of the corresponding isotropic absorption (u.v.) spectra, however, probably reveals an important difference in intensity of the bands situated in both cases at 200–210 nm, which should be taken into consideration. Too often ORD and CD data appear in literature without accompanying data on the isotropic absorption, making a certain designation of the various bands difficult.

A. Theoretical Aspects

The weak electrically forbidden magnetically allowed absorption of the saturated carbonyl group near 290 nm is well known and has been extensively explored both experimentally and theoretically. This $n \rightarrow \pi^*$ transition band arises from a promotion of one of the lone pair of electrons (n) on the oxygen atom to a vacant antibonding π^* orbital. At shorter wavelengths (185–195 nm), a second stronger band of high intensity appears, which has been attributed to an $n \rightarrow \sigma^*$ transition, although a $\pi \rightarrow \pi^*$ transition may also be involved[9,10]. The latter is usually considered to be situated at shorter wavelengths, perhaps around 150 nm.

The effect of attaching an electron-donating substituent such as halogen, $-NR_2$ or $-OR$ directly to the carbonyl carbon is to raise both the π and π^* levels, but the π level will be raised more[11]. The n level is largely unaffected or somewhat lowered, as illustrated in Figure 1[12]. This should result in a considerable blue-shift

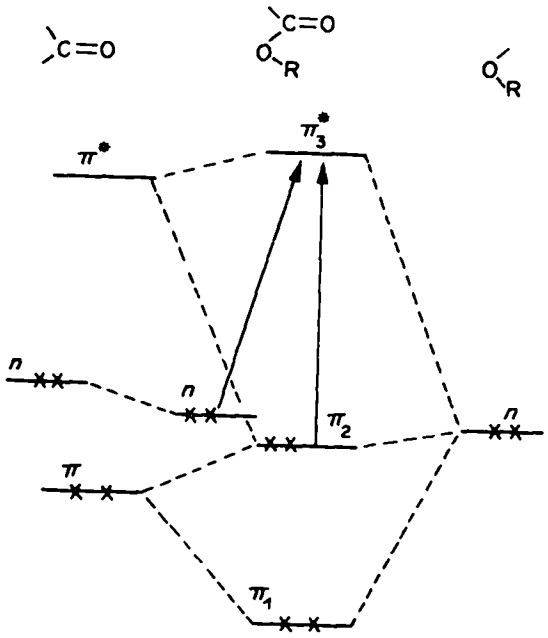


FIGURE 1. Energy level scheme for the ester chromophore. Reprinted with permission from W. D. Closson and P. Haug, *J. Amer. Chem. Soc.*, 86, 2384 (1964). Copyright by the American Chemical Society.

of the $n \rightarrow \pi^*$ transition to higher energies and a red-shift of the $\pi \rightarrow \pi^*$ transition, bringing the two absorption bands closer to each other. The $n \rightarrow \sigma^*$ transition often seems to have been overlooked in the discussion, but is apparently displaced to higher energies like the $n \rightarrow \pi^*$ transition. Calculations have placed it at 150 nm in the amide chromophore[13,14] but the presence of an $n \rightarrow \sigma^*$ transition between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions has also been considered[15,16].

B. Experimental Evidence

Some experimental facts which support the view in Figure 1 have been collected in Tables 1 and 2. Compared to acetaldehyde, the low intensity $n \rightarrow \pi^*$ transition band is shifted to 280 nm in acetone (hyperconjugation), to 235 nm in acetyl chloride and to 204–211 nm in acetic acid and ethyl acetate. The peak of the short wavelength high-intensity $\pi \rightarrow \pi^*$ (or the $n \rightarrow \sigma^*$) transition band is not accessible for these compounds in solution with ordinary instruments, but may be reached in the case of secondary and tertiary amides due to a further red-shift caused by the alkyl substitution on nitrogen. The vacuum ultraviolet spectra of formic and acetic acids, revealing these lower-lying bands, have been studied by many authors, recently by Bell and coworkers[28], and the vacuum ultraviolet spectrum of alanine in hexafluoroisopropanol has also been recorded[16] (Section IV.A.1.c).

The $n \rightarrow \pi^*$ transition of amides is often obscured by the band at shorter wavelengths. It may be observed as a shoulder at 225–235 nm in hydrocarbon

TABLE 1. Transitions in $CH_3C(O)R$

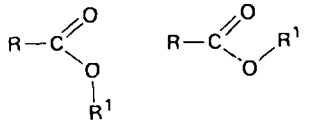
R	Solvent[a]	$n \rightarrow \pi^*$		$\pi \rightarrow \pi^*$		Reference
		λ_{max} (nm)	ϵ	λ_{max} (nm)	ϵ	
H	h	293	12			11
CH_3	h	280	14.5	188[b]	1860	17, 10
	w	265	18.5			17
Cl	h	235	53			11
	h	240	34.5			18, 19
NH_2	c	225		<180		20
	w	214		182	7600	11, 20
$NHCH_3$	c			184	5400	20
	w			186	8800	20
$N(CH_3)_2$	c			196	6850	20
	w			196	9350	20
$N(C_3H_7)_2$	c			202	7200	20
	w			200	9300	20
OC_2H_5	i	211	58			12
	w	204	60			21, 11
OH	h	205		175		22, 23
	w[c]	204	38			17
O^-	w	No maximum above 197 nm (ϵ ca 500)				17

[a]Solvents: h = hexane or heptane, c = cyclohexane, i = isooctane and w = water.
[b]Designed as an $n \rightarrow \sigma^*$ transition.
[c]Aqueous 10^{-2} M H_2SO_4.

solvents. In aqueous solution it is usually not perceivable due to the strong blue-shift caused by polar solvents (see acetone and ethyl acetate in Table 1), but the band has been suggested to lie at about 212 nm for most amides[20]. In non-polar solvents λ_{max} was estimated to be at 223–227 nm for secondary amides and at 231–233 nm for tertiary amides and amide groups in rings[20].

In carboxylate anions, the $n \rightarrow \pi^*$ transition band near 200 nm is usually also obscured depending on a red-shift or broadening of the lower-lying, more intense band, and a blue-shift of the $n \rightarrow \pi^*$ transition to higher energies on ionization[29]. This band was first revealed by CD measurements[30].

The effect of conformation [*s-cis* (**1a**), or *s-trans* (**1b**)] on the electronic absorption spectrum of the carboxyl group was studied by Closson and co-workers[26].



(1a) (1b)

From Table 2 the effect of substitution of the methyl group of acetic acid is evident. α-Substituents cause a red-shift of the $n \rightarrow \pi^*$ transition, which means that in several compounds with a chiral α-carbon the corresponding CE may be found at about 225 nm. In the case of the important α-hydroxy and α-amino acids, however, the red-shift is less. The latter compounds, as is well known, may have the special zwitterion structure. Corresponding red-shifts may be observed for the $\pi \rightarrow \pi^*$

TABLE 2. The effect of substitution, ring-closure and unsaturation on carboxylic transitions

Compound	Solvent[a]	λ_{max}(nm)	ϵ	Reference
Propionamide	w	210(sh)	150	17
Lactic acid	w	210	70	24
2-Chloropropanoic acid	e	220	85	25
N,N-Diethyl-2-chloropropionamide	e	214[b]	5760	25
	i	214[b]	4960	25
2-Bromopropanoic acid	e	228	300	25
	i	226	370	25
Propiolactone (β-lactone)	i	207	54	12
	m	204.5	49	12
	w	201	52	12
Butyrolactone (γ-lactone)	i	214	25	12
	m	208	40	12
	w	203(sh)	42	12
Valerolactone (δ-lactone)	m	214	55	26
Succinimide	a	244	76	
		221	125	17
	w	238	87	
		210(sh)		
		193[b]	19,400	17
N-Methylsuccinimide	c	245	105	
		222	210	
		199[b]	15,800	17
	w	235	125	
		201[b]	17,400	17
Glutarimide	w	250(sh)	80	
		230(sh)	350	
		201[b]	18,000	17
Ethyl acrylate	i	243	70	
		192[b]	14,200	27
Crotonic acid	w[c]	250(sh)	250	
		210[b]	12,800	17
Ethyl crotonate	i	202[b]	15,600	27
3-Methylcrotonic acid	w[c]	221[b]	12,200	27
Diethyl fumarate	i	260(sh)	250	
		210[b]	17,000	27
Diethyl maleate	i	194[b]	11,700	27

[a] Solvents: c = cyclohexane, i = isooctane, a = acetonitrile, e = ethanol, m = methanol and w = water.
[b] $\pi \rightarrow \pi^*$ transition.
[c] Aqueous 10^{-2} M H_2SO_4.

transition of substituted amides, for example to 214 nm in the case of *N,N*-diethyl-2-chloropropionamide[25]. Basch and coworkers[15] have reported the presence of a band of moderate intensity between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition bands of amides. This band was attributed to an $n \rightarrow 3s$ Rydberg excitation.

From Table 2 the effects of solvent, ring-closure and unsaturation are evident. Ring-strain obviously causes a blue-shift of the $n \rightarrow \pi^*$ transition. In imides, where two long wavelength low-intensity bands are observed, the first comes at relatively low energies. In α,β-unsaturated carboxylic acids and esters the $n \rightarrow \pi^*$ transition band is shifted to about 250 nm and the $\pi \rightarrow \pi^*$ band to 190–210 nm.

Also of interest in this connection is the 230 nm absorption of benzoic acid. The interpretation of this band as an intramolecular charge-transfer band, involving the

carboxyl group and the aromatic ring, by Tanaka[31], appears to have been widely accepted. An alternative interpretation[11] might be the entirely aromatic ^1L_a band (Platt's notation[32]). In any case, the 230 nm transition was found[31] to be long-axis polarized (recently verified by linear dichroism measurements by Nordén[33]), which is of importance for the use of the so-called exciton chirality method[34] (Section IV.B.2.b).

For the application of similar methods to biopolymers, knowledge of the polarizations of the amide transitions is of interest, especially that of the magnetic dipole forbidden, electric dipole allowed $\pi \rightarrow \pi^*$ transition. The $\pi \rightarrow \pi^*$ transition moment forms an angle of about 9° with the nitrogen–oxygen axis[39]. The conditions of the amide transition moments are further presented in connection with the $m_1\mu_2$ mechanism in Section III.A.4.a and are illustrated in Figure 9. Due to dipole–dipole couplings in α-helical polypeptides, the $\pi \rightarrow \pi$ transition is split into two transitions with long-axis and short-axis polarization, respectively[35–38] (Section IV.A.1.d)

III. CHIROPTICAL PROPERTIES OF LACTONES AND LACTAMS

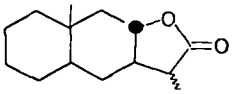
Since lactones and lactams are relatively rigid molecules, they have attained special interest, and several efforts have been made to formulate rules for the correlation of their geometries and chiroptical properties. The great success of the well-known octant rule for the carbonyl $n \rightarrow \pi^*$ transition CE[1–6,40] has been a stimulus. However, the basic symmetry of the carbonyl group is C_{2v}, whereas the only symmetry element of the carboxyl, ester and amide groups is a σ plane[41]. (The carboxylate anion has C_{2v} symmetry; see Section IV.A.1.c.) This seriously complicates the situation and necessitates the application of some approximations. The rules for the prediction of the signs of the lactone and lactam $n \rightarrow \pi^*$ CE from geometry are given below.

A. Saturated Lactones and Lactams

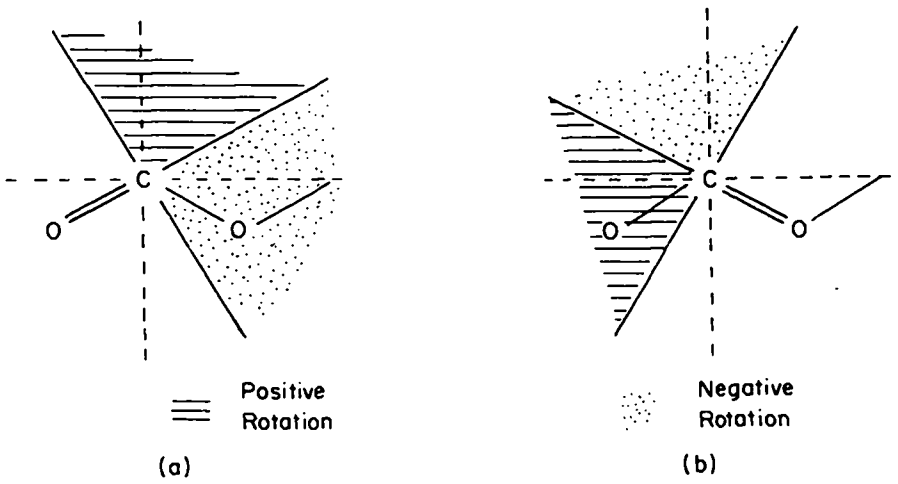
1. *Sector rules*

a. The sector rule of Klyne and coworkers. This first approach, made by Jennings, Klyne and Scopes[42] in 1965, is directly based on the carbonyl octant rule[40]. The approximation was made that both carbon–oxygen bonds have some double-bond character and that they are equivalent. Symmetry planes are then the —C—CO—O— plane and the plane bisecting the $\widehat{OCO}$ angle. The carbonyl octant rule is applied to each carbon–oxygen bond (Figure 2, a and b) and the two diagrams are superimposed to give a sector diagram (Figure 2c) in which the separate contributions cancel in certain sectors (A, C, D, F) and add in others.

In order to predict the signs it is necessary to consider two views of the molecule: (*a*) The view along the bisector of the $\widehat{OCO}$ angle to determine which perturbing parts of the molecule are situated above and below the plane of the lactone group. (*b*) The view from above the projection of the molecule on the plane of the lactone ring to determine in which sectors the various atoms and bonds fall. The eudesman lactone derivative (2) in Figure 3 is given as an example for which a



(2)



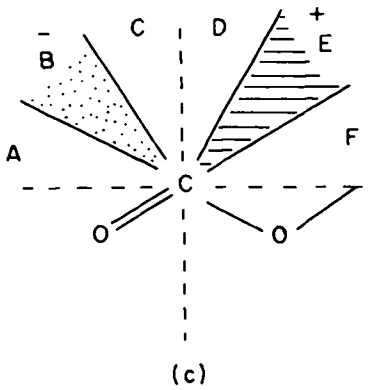


FIGURE 2. (a) and (b) Derivation of the section rule; (c) rule of Klyne and coworkers. After J. P. Jennings, W. Klyne and P. M. Scopes, *J. Chem. Soc.*, 7211 (1965). Reproduced by permission of the Chemical Society, London.

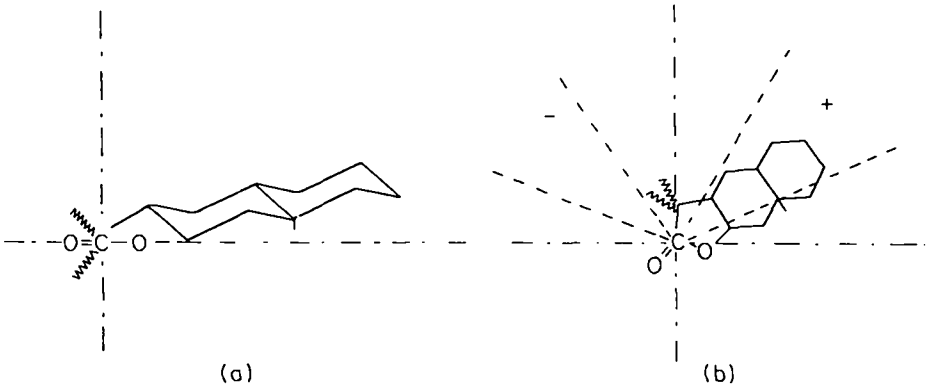
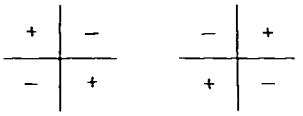


FIGURE 3. Application of the sector rule of Klyne and coworkers. Both $C_{(\alpha)}$ epimers are represented. After J. P. Jennings, W. Klyne and P. M. Scopes, *J. Chem. Soc.*, 7211 (1965). Reproduced by permission of the Chemical Society, London.

positive CE is predicted [independent of the configuration at $C_{(\alpha)}$] in accordance with experimental observations[42].

The signs given in Figure 3 are those of the back upper sectors. The back lower sectors have the opposite signs. Atoms near the sector boundaries may make small contributions. The result may be described as an octant projection in a view along the $\widehat{OCO}$ angle bisector, which is similar to that of the ordinary carbonyl octant rule, but *the signs are reversed:*



The rule was applied to a great number of steroid lactones[42-45] and, like the following one, also to some ε-caprolactones[46]. During the past twelve years since the rule was formulated some of its imperfections have been revealed, and further work on its improvement is in progress[47].

b. The 'Comet Rule' of Snatzke and coworkers. This rule was deduced in general for chromophores of the type $-X-Y=Z- \leftrightarrow -X=Y-Z-$, and was first

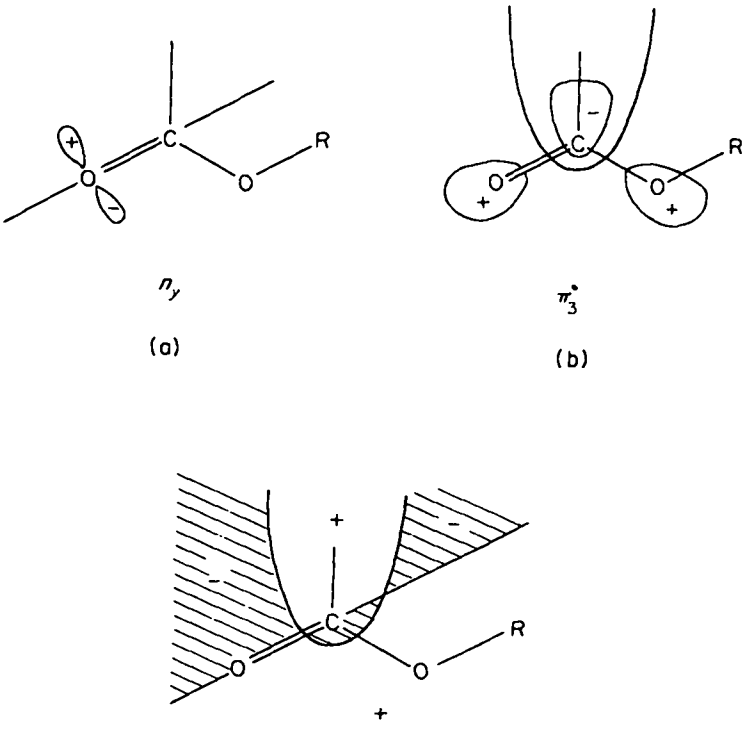
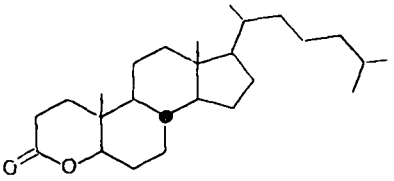
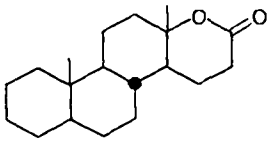


FIGURE 4. Node planes of (a) the n_y and (b) the π_3^* orbitals of the lactone chromophore; (c) the sector rule of Snatzke and coworkers. After G. Snatzke and coworkers, *Tetrahedron* **22**, 3103 (1966). Reproduced by permission of Pergamon Press Ltd.

formulated for the nitro chromophore[48]. It is based on the nodal surfaces of the n_y and π_3^* orbitals involved in the lactone $n \rightarrow \pi^*$ transition[12] (Figure 4; cf. Figure 1). In Figure 4(c) the signs for the upper sectors are shown. The lower sectors have the opposite signs. This rule overestimates the differences between the two lactone oxygens, whereas the former one overestimates the similarities. However, it could explain why the two lactones (3) and (4) both exhibit a positive CE[48].



(3)



(4)

c. Sector rules of Weigang and coworkers. Weigang and coworkers[49] use dynamic coupling theory to derive the sector rules for lactones and lactams. The chromophores are considered as modified carboxylate anions. The result is an octant rule for lactams with ordinary signs (compared with the octant rule for ketones) and an octant rule for lactones with the opposite signs. As in the preceding cases two views are considered: one view along the $\widehat{OCO}$ angle bisector and one from above.

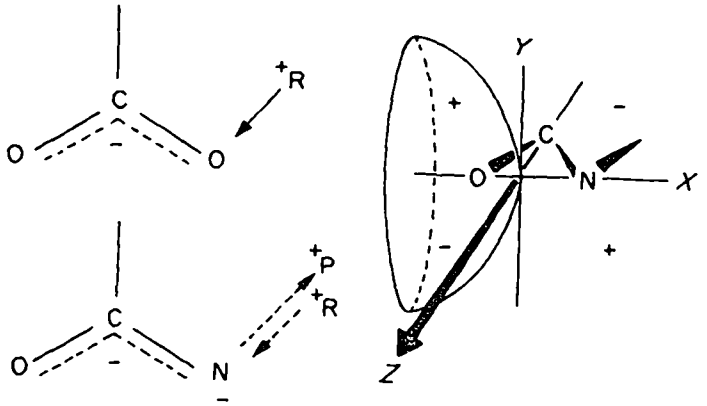


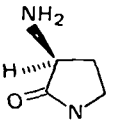
FIGURE 5. The sector rule of Weigang and coworkers for the lactam chromophore. Taken from O. E. Weigang, Jr. in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism* (Eds. F. Ciardelli and P. Salvadori), Heydon, London, 1973. Reproduced by permission of Heydon & Son Ltd.

The sector rule for the lactam $n \rightarrow \pi^*$ CE is illustrated in Figure 5. The curved surface is a spherical distortion of the *YZ* surface of the octant rule nodal planes. The signs refer to the back octants.

Klyne and Scopes[21] have collected CD data on pairs of lactones and the corresponding lactams, which suggest that in the case of rigid compounds the two classes of compounds have oppositely signed $n \rightarrow \pi^*$ CE, as these rules predict. Flexible compounds, however, may have the same sign. (See also Section III.A.3.)

d. The quadrant rule of Litman and Schellman. Lactams and diketopiperazines[50,51] have attained special interest since they may serve as model compounds

for the peptide linkage. Litman and Schellman[52] chose the γ-lactam obtained from 2,4-diaminobutyric acid, L-3-aminopyrrolid-2-one (5) for this purpose in an



(5)

investigation of the $n \rightarrow \pi^*$ CE of peptides. In combination with previous theoretical work[53], a quadrant rule for the peptide bond was found (Figure 6). The signs are those to be anticipated for a positive source of potential in the given quadrant. For a negative source of potential the signs are reversed. In combination with theoretical calculations of ring geometries, the rule was shown to be valid for a series of methylpyrrolid-2-ones[54], and in this connection an apparent anomaly of 3-methylpyrrolid-2-one, previously studied by Greenfield and Fasman[55], was resolved and shown to depend on a misprint in a configuration assignment.

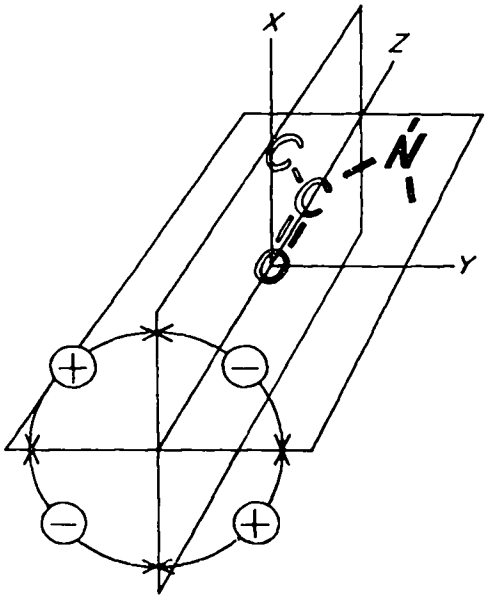


FIGURE 6. The quadrant rule of Litman and Schellman for the peptide bond. Reprinted with permission from B. J. Litman and J. A. Schellman, *J. Phys. Chem.*, 69, 978 (1965). Copyright by the American Chemical Society.

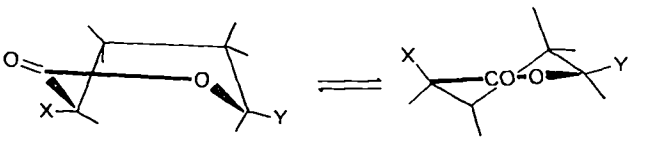
That a γ-lactam may be a suitable model for the study of peptide CD was demonstrated by Urry[56], who obtained CD curves closely resembling those of helical polypeptides from L-5-methylpyrrolid-2-one in non-polar solvents. A dimer was proposed to partly explain the rather different appearance of these spectra compared to that for water solution.

2. *Ring chirality rules*

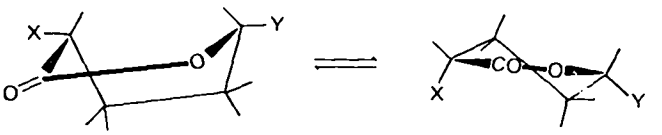
a. Chiral spheres. In most lactones the ring itself is chiral and several research groups have proposed rules for the correlation of ring chirality and the sign of the $n \rightarrow \pi^*$ CE. In the approach of Snatzke and coworkers[57,58] for the generation of rotational strengths from chiral systems in the general case, a given molecule is divided into spheres. The first sphere is the chromophore itself, the second sphere consists of rings and substituents attached to the chromophore, the third sphere is the rings and substituents on the second sphere, etc. If the first sphere is chiral, as in for example hexahelicens and twisted dienes or α,β-unsaturated lactones, this chirality determines the signs and intensities of the dichroic bands. When the first sphere is achiral as in ketones, lactones and carboxylic acids, and the second sphere is chiral, as may be the case in lactones, the chirality of this second sphere should determine the chiroptical properties. If the lactone ring is planar as may be the case in some five-ring lactones, rigidly fused to other rings, third-sphere chirality determines the sign of the CE, etc.

Indeed, chirality rules mean that the spatial positions of certain perturbing atoms determine the CD, and thus it should in principle be possible to translate them into sector rules. However, a chirality rule is often easier to use.

b. The chirality rules of Wolf for δ-lactones. These rules were formulated in 1966 on the basis of the observations made with X-ray analyses that in most lactones the group —C—CO—O—C— is planar, leading to a preferred boat or, alternatively, half-chair conformation of the δ-lactone ring[59]. The CD extremum of the latter conformation usually lies at longer wavelengths than that of the corresponding boat form. The rules correlate the chiralities of these conformations with the signs of the $n \rightarrow \pi^*$ CEs (6 and 7). The form preferred by a particular molecule is determined by junctions to other rings and/or the substitution pattern[59]. The experimental work was carried out on steroid lactones.

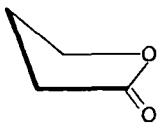


(6a) Positive CE (6b) Negative CE

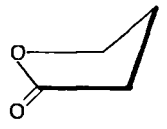


(7a) Negative CE (7b) Positive CE

c. The chirality rules of Beecham for γ-lactones and γ-lactams. In γ-lactones the planarity of the lactone —C—CO—O—C— group leads to an envelope-type conformation, with the fifth ring-atom $C_{(\beta)}$ situated above or below the plane. Okuda and coworkers[60] noted that the sign of the $n \rightarrow \pi^*$ CE was related to the substituent pattern at $C_{(\alpha)}$, which was confirmed by Beecham[61] in the case of γ-lactones derived from sugars. Beecham suggested[61,62] that in fact the configuration at $C_{(\alpha)}$ determines the position of $C_{(\beta)}$, i.e. the chirality of the lactone ring, which in turn determines the sign of the CD effect. [The influence of $C_{(\alpha)}$ substituents is further considered in Section III.A.3.] With the chirality rule illustrated by 8 and 9, all previous observations of γ-lactone CEs could be



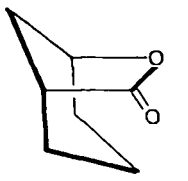
(8) Positive CE



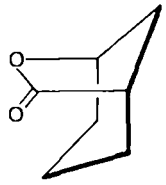
(9) Negative CE

explained[62], including those of the eudesman lactone (2) and its $C_{(\alpha)}$ epimer which, as mentioned in Section III.A.1.a, both exhibit positive CEs independent of the absolute configuration at the carbon adjacent to the chromophore. The ring chiralities are however the same (cf. Figure 3).

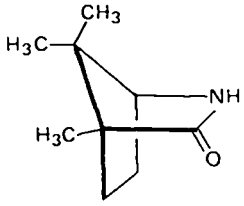
Rules have also been given for bridged lactones[62,63]. Comparisons of **10** and **11** with **8** and **9** reveal that in the case of the bicyclo[3.2.1]octane skeleton the signs related to the chirality of the five-membered γ-lactone ring are reversed relative to the unbridged compounds. According to these rules, bridged lactones and lactams should have the same sign of the $n \rightarrow \pi^*$ CE as deduced[63] from camphorolactams **12** and **13**.



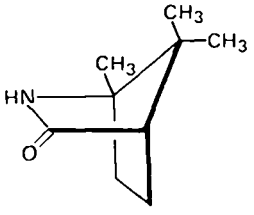
(10) Negative CE



(11) Positive CE



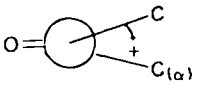
(12) Negative CE



(13) Positive CE

Beecham made the interesting observation that the numerical values of the dissymmetry factor $\Delta\epsilon/\epsilon$ were constant within certain groups of lactones[61,63]. These factors may be considered as normalized rotational strengths and their constancy was taken as evidence for a constant source of dissymmetry in the transitions within each group, independent of substitution or solvent, but dependent on a common skeletal structure. Thus Goodman and coworkers[64] found that lactams **12** and **13**, in each of three solvents, exhibit CD curves which are mirror images, despite the different positions of the bridgehead methyl groups.

d. The chirality rule of Legrand and Bucourt. These authors[65] proposed a simple rule for 5–7-membered lactones in terms of the dihedral angle of the group —C—CO—O—C, which consequently cannot be situated exactly in one plane as more or less presupposed in the above rules. The molecule is viewed along the —CO—O— bond as shown in projections **14** and **15**, and the sign of the $n \rightarrow \pi^*$ CE is



(14) Negative CE

(15) Positive CE

opposite that of the dihedral angle mentioned. This angle is positive when the proximate bond is rotated in a clockwise direction to eclipse the remote bond. In other words, this implies a positive helicity. The dihedral angles formed by the sides of a cyclic molecule have a characteristic sequence of signs for each conformation[65].

The rules of Legrand and Bucourt were used by Korver[66] to determine the stereochemistry of (*S*)-(+)-5-decanolide and (*S*)-(+)-5-dodecanolide, (**6**, X = H and Y = pentyl and heptyl respectively). The CD spectra exhibit solvent- and temperature-dependent bisignate curves (this term was proposed by Klyne and Kirk[9]), a negative band near 240 nm and a positive band near 210 nm (Figures 7 and 8).

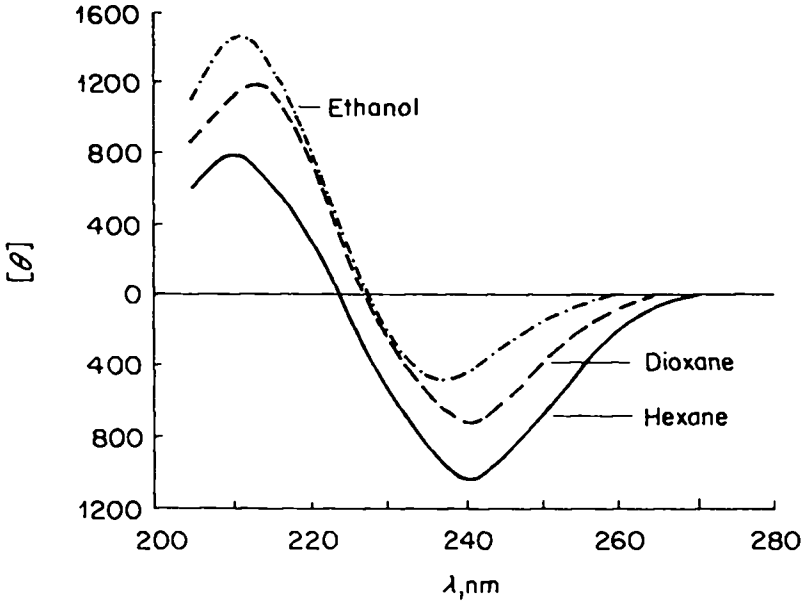
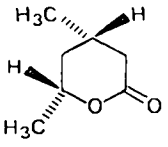


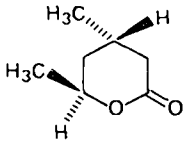
FIGURE 7. CD spectra of 5-decanolide in hexane, dioxane and ethanol. Taken from O. Korver, *Tetrahedron*, **26**, 2391 (1970). Reproduced by permission of Pergamon Press Ltd.

(Bisignate curves had previously also been observed by Wolf with steroid lactones[59].) The spectra were interpreted as arising from a conformational equilibrium of the boat conformation (**6a**) and the half-chair conformation (**6b**), the latter being the more stable and consequently dominant at low temperatures (Figure 8).

Carroll and coworkers[67] and Snatzke and coworkers[68,69] have also used the rules of Legrand and Bucourt for conformational analyses of δ-lactones. These rules allow the sign of a CE to be predicted for conformations other than boat and half-chair, which was taken advantage of by Carrol and coworkers in analysing the CD spectra of dimethylvalerolactones **16** and **17**. These are $C_{(5)}$ epimers, and both exhibit a negative 220 nm CD band.



(16)



(17)

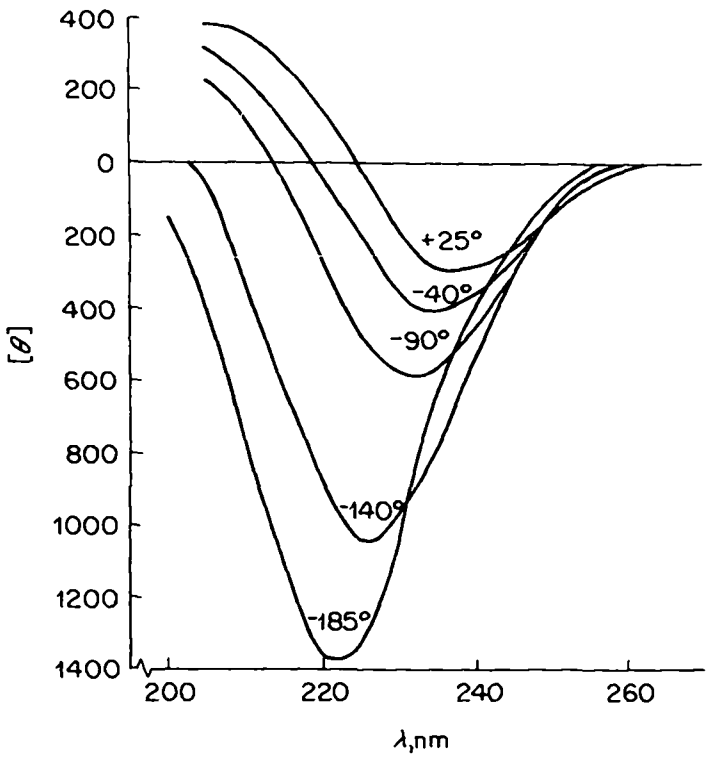
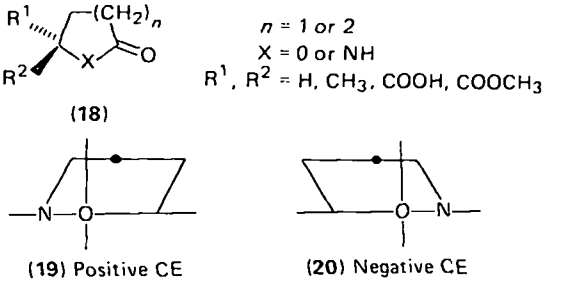


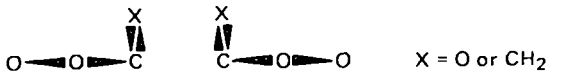
FIGURE 8. CD spectra of 5-decanolide at various temperatures, measured in EPA (diethylether:isopentane:ethanol = 5:5:2). Taken from O. Korver, *Tetrahedron*, **26**, 2391 (1970). Reproduced by permission of Pergamon Press Ltd.

Červinka, Snatzke and coworkers[69] studied similar monocyclic γ- and δ-lactones and -lactams (**18**) and in some cases bisignate curves were observed. The authors concluded that the ring helicity rules could be applied to the five-membered lactams as well.

e. The chirality rule of Ogura and coworkers for ε-lactams. This rule, shown by structures **19** and **20**, was proposed for ε-lactams but was also applied to four-membered, five-membered and six-membered lactam rings[70-72].



f. Chirality rules for α,β-cyclopropyl and α,β-epoxy lactones. For these compounds, rules illustrated by structures **21** and **22** have been formulated by

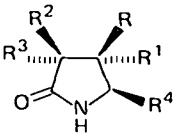


(21) Positive CE (22) Negative CE

Snatzke and coworkers[73-75]. The rules are similar to those for the corresponding cyclopropyl and epoxy ketones[74], and they are reminiscent of the chirality rules for α,β-unsaturated lactones, which may indicate that the small fused rings have an effect on the $n \rightarrow \pi^*$ CE similar to that of a double bond (Section III.B.1).

3. *The influence of $C_{(\alpha)}$ substituents*

In order to clarify the influence of $C_{(\alpha)}$ substituents, Meguro and coworkers[76] studied the CD of trimethylsilyl derivatives of aldonic acid γ-lactones, They reached the conclusion that $C_{(\alpha)}$ substituents and ring conformation both contribute to the $n \rightarrow \pi^*$ CE. This was further investigated and discussed in the case of other lactones[77] and lactams[78,79]. The Japanese research group showed that the axial haloketone rule[80,81] could be applied to lactones and lactams and they suggested the promotion of a strong and inherently dissymmetric chromophore due to the interaction between the lone-pair electrons of the $C_{(\alpha)}$ axial halogen (or other substituent with lone-pair electrons) and the carbonyl π electrons of the lactone or lactam group. (Similar deductions were drawn from some theoretical calculations; see Section III.A.4.b).



(23) $R = R^2 = R^4 = H$, $R^1R^3 = OCMe_2O$
(24) $R = R^2 = R^4 = H$, $R^1 = R^3 = OH$
(25) $R = R^1 = Me$, $R^2 = R^4 = H$, $R^3 = OH$
(26) $R = R^1 = R^3 = R^4 = H$, $R^2 = NH_2$
(27) $R = R^1 = R^3 = R^4 = H$, $R^2 = N^+H_3\ Cl^-$
(28) $R = R^1 = R^2 = R^4 = H$, $R^3 = Me$
(29) $R = R^1 = R^2 = R^3 = H$, $R^4 = Me$

For example, in the case of the γ-lactams **23** – **29**[79] the CD signs of **27** – **29**, which have no $C_{(\alpha)}$ substituents, are assumed to be determined by ring chirality according to Beecham's rule. In the CD spectra of **23** – **26**, red-shifts of 1–11 nm relative to **29** were observed, indicating interactions of the lactone group and the $C_{(\alpha)}$ substituents. The CD sign, being the same for the lactams and corresponding lactones, were proposed to be determined by the $C_{(\alpha)}$ substituents from the formation of an inherently dissymmetric chromophore. The magnitude in the cases of **23** – **26** could be explained by combined contributions from the $C_{(\alpha)}$ substituents and the ring chiralities. Thus, in **24** – **26** the addition of two factors of opposite signs results in relatively small molar ellipticities and, in the case of **25**, different signs for water and methanol solutions. Similar observations were made on δ-lactones[78].

Novák[82] has studied the effect of further branching at $C_{(\alpha)}$ by introducing a methyl group at this position in γ-lactones derived from sugars. In all cases a decrease of the absolute CD values was observed, but not to such an extent as to cause a change of the sign. This was explained in terms of a dynamic equilibrium of two conformers (i.e. ring chiralities) due to a competition between the methyl and hydroxyl groups for a pseudoequatorial orientation.

4. Theoretical considerations

a. The '$m_1\mu_2$ mechanism'. This mechanism for the generation of rotational strength by coupling of a magnetically allowed transition in one chromophore and an electrically allowed transition in another has been considered important in compounds with two identical chromophores in a special geometric arrangement. It has been used chiefly for diketopiperazines (models for the peptide bond[50]) and other cyclic peptides[51], but was considered also by Woody and Tinoco[13] in the case of peptide helices. The coupling in amides takes place by way of the interaction of μ_2, the electric transition moment of the $\pi \rightarrow \pi^*$ transition of chromophore 2, with the quadrupole associated with m_1, the magnetic transition moment of the $n \rightarrow \pi^*$ transition of chromophore 1 (Figure 9). In substituted diketopiperazines the molecule is folded along the dotted line of Figure 9. It was concluded that this mechanism and the one-electron ($m_1\mu_1$) mechanism are equally important for peptide CD and that their relative dominance is a matter of geometry rather than principle[51].

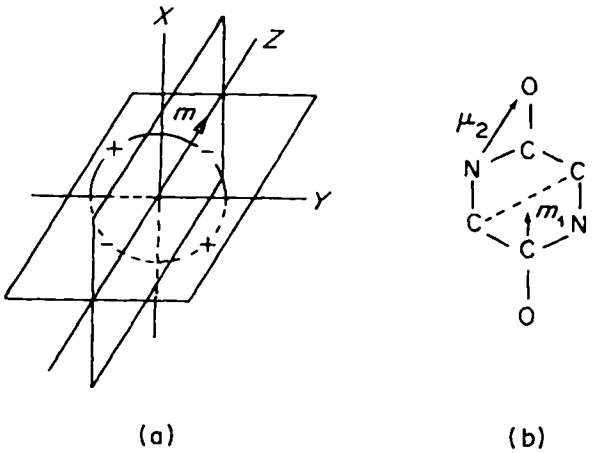
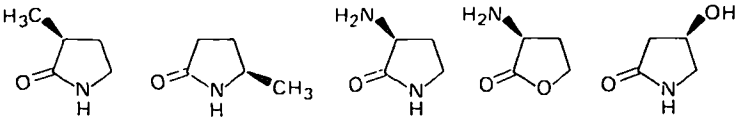


FIGURE 9. The $m_1\mu_2$ mechanism. (a) Quadrupole and magnetic moments of the $n \rightarrow \pi^*$ transition; (b) the interaction of μ_2 with m_1 in diketopiperazine. Taken from W. Klyne and P. M. Scopes in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism* (Eds. F. Ciardelli and P. Salvadori), Heydon, London, 1973. Reproduced by permission of Heydon & Son Ltd.

b. Calculations of rotational strengths. During recent years, theoretical calculations on the optical activities of γ- and δ-lactones and -lactams have been performed by Richardson and coworkers[83-85], by Geiger and Wagnière[86], and by Volosov and coworkers[87]. Using the INDO MO model for their calculations, Richardson and coworkers found that the signs and the magnitudes of the $n \rightarrow \pi^*$ CEs are sensitive to the ring conformation as well as substitution, and the contributions from the two sources could be separated (cf. Section III.A.3). In α-substituted (—OH, —NH_2) and α,β-disubstituted (—OH) γ-lactones, the CEs reflect the absolute configuration at $C_{(\alpha)}$, supporting the experimental findings of Beecham[61-63], and of Meguro and coworkers[76-79]. The calculations revealed a significant admixture of -substituent orbitals into the *n* molecular orbital, as was

also suggested by Meguro and coworkers. In the case of δ-lactones only the half-chair and the boat conformations were taken into account, but the results agreed well with conclusions reached by Korver[66], Beecham[61–63], Legrand and Bucourt[65] and Wolf[59,88].

Geiger and Wagnière[86] used the CNDO/CI method for calculations of the rotational strengths of compounds **30 – 34**. (Compounds **30 – 32** were also considered by Richardson and coworkers[85].) They could correctly predict the signs of the $n \rightarrow \pi^*$ CEs, and found that Schellman's quadrant rule for the amide chromophore was obeyed (see Section III.A.1.d). In relevant parts these results and the INDO results of Richardson and coworkers[85] were similar.



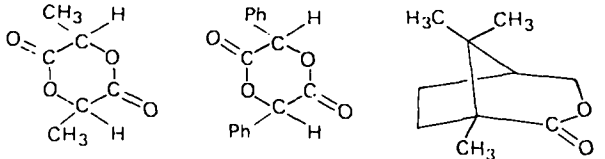
(30) (31) (32) (33) (34)

Volosov and coworkers[87] also calculated the rotatory strengths of 3- and 5-methylpyrrolid-2-ones (**30** and **31**) using the CNDO/S method, and arrived at the conclusion that the ring conformation significantly affects both the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ transitions.

5. Some further aspects of lactone CD

Meguro and coworkers[89] have developed a method to determine the relative configuration at $C_{(\alpha)}$ in aldonic acid γ-lactones from the CD of the borate complexes obtained on chelate formation between borate ions and vicinal *cis* diols. Chelate formation between *cis* $C_{(\alpha)}$ and $C_{(\beta)}$ hydroxyls was detected by a red-shift and a decrease in the molar ellipticities of the $n \rightarrow \pi^*$ CE when the measurements were performed on borate buffer solutions.

Toniolo and coworkers[90] investigated some mono and bicyclo lactones (**35–37**). (*S*,*S*)-(**35**), which exhibits a negative CE, may be considered as a cyclic form of methyl *O*-acetyl-(*S*)-lactate, which has a positive CE. This inversion in sign was not observed in the case of *N*-acetyl-(*S*)-alanineamide relative to its cyclic form (*S*,*S*)-alaninediketopiperazine[91]. The possibility of rationalizing the CD of the lactides by the $m_1\mu_2$ mechanism (Section III.A.4.a) was pointed out by Klyne and Scopes[21]. The rigid bicyclic compound (**37**) exhibits three CD bands at 190–250 nm in trifluoroethanol, and the possibility of an $n \rightarrow \sigma^*$ transition between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions is discussed[90].



(35) (36) (37)

The chiroptical properties of azlactones, derived from *N*-acetoacetyl amino acids, have been investigated[92,93]. These azlactones, for which several isomeric forms are theoretically possible, exhibit absorption bands in the 260–300 nm region, and from the associated CD bands structural and stereochemical assignments can be made[92].

Overberger and Weise[94] have investigated the ORD of some thiepan-2-ones. These ε-thiolactones contain the acylthio chromophore, which is further presented in Section IV.A.1.d.

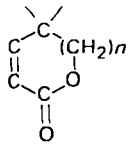
B. Unsaturated Lactones

α,β-Unsaturated lactones usually exhibit two CEs at easily accessible wavelengths above 190 nm; one CE is associated with the $n \rightarrow \pi^*$ transition at 245–275 nm [95,96] and one is associated with the $\pi \rightarrow \pi^*$ transition at 205–235 nm[96]. In the case of β,γ-unsaturated lactones a significant increase in the intensity of the 220 nm $n \rightarrow \pi^*$ CE has been observed; for example, molar ellipticities of about 80,000 have been obtained, compared with about 5000 for related saturated compounds[97]. Similar results have been obtained on the chiroptical spectra of β,γ-unsaturated ketones[81].

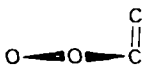
Unsaturated lactams appear to have been little investigated.

1. Chirality rules for the n → π CE of butenolides and pentenolides*

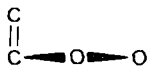
Chirality rules for the correlation of the $n \rightarrow \pi^*$ CE and geometry of α,β-unsaturated γ-lactones (butenolides) and δ-lactones (pentenolides) were first given by Snatzke and coworkers[73,74,98] and subsequently revised by Beecham[99,100]. These rules were direct transfers of similar correlations for α,β-unsaturated ketones. It was stated by Snatzke and coworkers that for butenolides (**38**) ($n = 0$) the sign of the CE should be the opposite to that for six-membered ($n = 1$) rings with the related chirality; i.e. according to this, for $n = 0$ the signs given for **39** and **40** should be altered.



(38)

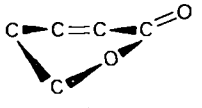


(39) Positive CE

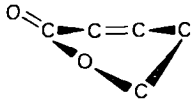


(40) Negative CE

Beecham[99,100] pointed out that in the rule above it is presumed that the group —C—CO—O—C— is planar, whereas X-ray analysis has shown that neither this group, nor the enone system is planar in the pentenolide ring.[101]. Carbon atoms 1–4, however, are situated in a common plane with the fifth carbon atom displaced 0.6–0.7 Å out of the plane. The ring oxygen is slightly displaced to the same side as $C_{(5)}$ and the carbonyl oxygen is slightly displaced to the opposite side. This results in the existence of two enantiomeric conformations (**41** and **42**). (These are not well represented by Dreiding models[100].)



(41)



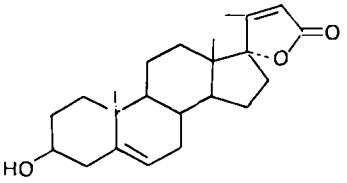
(42)

Despite the smaller chiral sense of the —C=C—C=O system in this real conformation compared to the model of Snatzke and coworkers, the pentenolide rule of the latter authors was found to be valid. In Beecham's formulation (which is equivalent to the rule illustrated by **39** and **40**) a left-handed chirality of the

—C=C—C=O group (43) is associated with a positive $n \rightarrow \pi^*$ CE and a right-handed chirality (44) with a negative CE.

(43) Positive CE (44) Negative CE

In the case of butenolides, however, Beecham arrived at a different conclusion. It was found that if the requirement of –C–CO–O–C– planarity was removed, stereomodels showed the handedness of the —C=C—C=O system to be reversed for the compounds (45 and 46) used by Snatzke and coworkers for the evaluation of the butenolide rule. Therefore the sign–chirality relationship should be the same as for pentenolides. Indeed, the butenolides are planar[102–104] and the introduction of a skewed enone system on models is a result only of accommodations of molecular features external to the ring, such as the minimization of interactions between groups.



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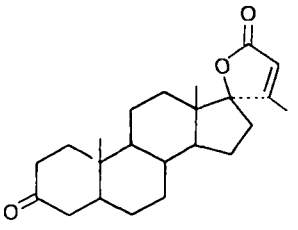
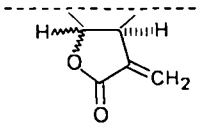


(46)

So far, *transoid* enone systems have been considered. Stöcklin and coworkers[95] investigated 44 α-methylene-γ-lactone sesquiterpenes with the structural feature shown in 47 and obtained good correlations of the $n \rightarrow \pi^*$ CE and the position and



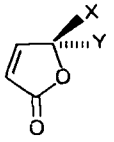
(47)

stereochemistry of the lactone ring fusion. Beecham[99,100] paid further attention to these *cisoid* —C=C—C=O systems and arrived at the conclusion that if chirality in the *transoid* system determines the sign of the $n \rightarrow \pi^*$ CE, the sign–chirality relationship is the inverse for the *cisoid* case. This might indicate a quadrant rule obedience.

2. *Rules for the $\pi \rightarrow \pi^*$ CE of α,β-unsaturated lactones*

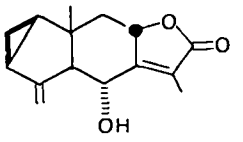
a. The γ-substituent rule for butenolides. This rule was formulated by Ushida and Kuriyama[96], who pointed out the ambiguity of the chirality rules discussed in the previous section when applied to the planar butenolides. According[96] to X-ray analysis, the maximum deviation of the –C=C–C=O torsional angle from 180° is 3.9°. The authors related the sign of the $\pi \rightarrow \pi^*$ CE to the substituent pattern at $C_{(5)} = C_{(\gamma)}$ in such a way that when the polarizability of substituent X in 48 is greater than that of Y the $\pi \rightarrow \pi^*$ CE at 205–235 nm is negative, and in the

reversed case positive. This rule was found to be valid for 20 investigated compounds[96], but failed for two, linderenolide (**49**) and its acetate, which possess allylic oxygen atoms. Their CD, however, could be explained in terms of the chirality rule for this type of compound (see next section).



X > Y; negative CE
X < Y; positive CE

(48)

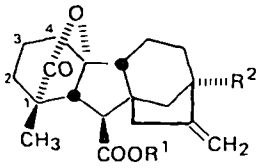


(49)

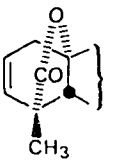
b. The allylic oxygen chirality rule. Allylic oxygen atoms have an overwhelming influence on the CD of olefins, dienes and enones[105-107], and a similar effect was observed in the case of ene-acids[106] and ene-lactones[100]. For the first $\pi \rightarrow \pi^*$ transition of these chromophores it was shown that a right-handed O–C–C=C– chirality was associated with a positive CE and a left-handed chirality with a negative CE. (It should be noted that this relationship is opposite to that illustrated by structures **14**, **15**, **43** and **44**.) In the case of linderenolide (**49**), mentioned in the previous section, the negative CE ($\Delta\epsilon = -24.1$) observed at 219 nm is compatible with the left-handed helicity of the O–C–C=C– system.

3. The chirality rule for β,γ-unsaturated lactones

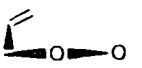
Meguro and coworkers[97] investigated the CD of a series of gibberellins with the general formula **50**. In the case of the 2,3-unsaturated compounds (β,γ-unsaturated ε-lactone) (**51**), an increase in intensity, but no wavelength shift, relative to the saturated compounds, was observed for the 220 nm $n \rightarrow \pi^*$ CE. A corresponding influence of a β,γ double bond or similarly positioned aromatic ring[81,108] was observed on ketones. For the latter chromophore, a chirality rule relating the sign of the $n \rightarrow \pi^*$ CE and geometry was formulated by Moscowitz and coworkers[81] and this rule was transferred to β,γ-unsaturated lactones by Snatzke and coworkers[73,74] (**52**–**53**). The negative 220 nm CEs observed for the gibberellins are compatible with this rule.



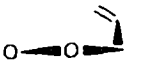
(50)



(51)



(52) Positive CE



(53) Negative CE

IV. CHIROPTICAL PROPERTIES OF CARBOXYLIC ACIDS, ESTERS, AMIDES, AND ACID CHLORIDES

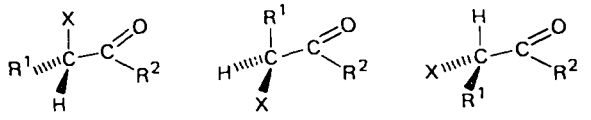
A. Aliphatic Compounds

1. α-Substituted carboxylic acids, esters and amides

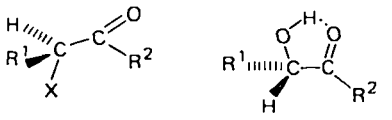
a. Conformations. Carboxylic acids and some of their derivatives have flexible structures, and the conformation of the chromophore relative to the rest of the

molecule is uncertain due to the free rotation around the bond to $C_{(\alpha)}$. However, the fact that dichroic absorption bands, in some cases of relatively high intensities, are observed for these compounds may be taken as evidence for a preferred conformation (or a few preferred conformation) of the carboxyl group. If any conformation could be attained and each were equally populated, application of a sector rule or chirality rule of any kind would reveal an extensive cancellation of the various effects. Low-temperature CD measurements of carboxylic acids[109-115] usually show an increase of the $n \rightarrow \pi^*$ CE with decreasing temperature, compatible with an equilibrium shift to the energetically most favoured conformer or rotamer. Conformational analyses of a great number of mainly steroid and diterpene carboxylic acids[116-119] have been made with the aid of the lactone sector rule of Klyne and coworkers (Section III.A.1.a), applied to acids.

In the case of α-substituted carboxylic compounds, $R^1CHXCOR^2$ (R^2 = OR, NR_2), X-ray diffraction and conformational analyses by various methods[25,120-126] have shown that in the two most preferred conformations (**54** and **55**) one of the bonds C–X or C–R^1 is eclipsed with the carbonyl part of the carboxylic group. The antiperiplanar conformation (**57**) (with respect to the C=O and C–X bonds) is also often considered, whereas the anticlinal (**56**) is regarded as energetically higher and less populated[112,115,120,127]. For example, rotamer **57** was taken into account in the case of halogenated amides[25]. For X = NHR or OH, rotamer **54** is considered to be the most favourable due to the possibility of hydrogen bonding to the carbonyl oxygen **58**, revealed by IR measurements as well[128]. However, this rotamer was also found to be the more stable in α-haloesters in solution[129]. In alkyl acids the $C_{(\alpha)}$–$C_{(\beta)}$ bond eclipses the carbonyl function[125,130-133] in the predominant conformation.



(54) Synperiplanar (55) (56) Anticlinal



(57) Antiperiplanar (58)

In recent years, several α-substituted acids and esters have been studied, especially α-amino[24,30,134-137], α-hydroxy[24,111,127,135,137-140], α-halogeno[25,115,138], α-trimethylammonium[141,142] α-mercapto[143] and α-alkyl[113,127,138,144] compounds. Frequently bisignate curves were observed, explained by some authors in terms of conformation equilibria, and by others in alternative ways. The discussion of the chiroptical properties of these compounds in the literature is not always limited to a particular α-substituent and therefore it is best accounted for under one heading:

b. The lactic acid anomaly. This section will summarize the controversial ideas and interpretations of the appearance of a long-wavelength CD band around 240 nm in addition to the expected band at shorter wavelength in the CD spectra of several α-substituted carboxylic acids, esters and amides. The phenomenon has been

named from the observations of Anand and Hargreaves[139], who in 1967 reported a low-intensity negative band ($\Delta\epsilon$ ca -5×10^{-3}) at 240–250 nm, depending on the solvent, in the CD spectra of (*S*)-lactic acid. Another more intense positive band was situated below 210 nm, and this was the only one which had been revealed previously by ORD[145-147]. The long-wavelength band disappeared in alkaline solution. It was interpreted by Anand and Hargreaves as associated with the $n \rightarrow \pi^*$ transition, and the short-wavelength band was considered as arising from the $\pi \rightarrow \pi^*$ transition of the carboxyl group.

In fact the presence of a weak ($\Delta\epsilon$ ca -2×10^{-2}) long-wavelength (237 nm) negative 'extra' band had been observed previously by Legrand and Viennet[30] in the CD spectra of the amino acids proline and hydroxyproline at pH 13. Characteristic for the natural L-series of amino acids is a positive band at shorter wavelength. The following values for alanine[30] may be representative (nm, $\Delta\epsilon$): 208, +1.04 at pH 1; 204, +0.68 at pH 7; 214, +0.33 at pH 14. The negative 237 nm band of proline was observed independently by Katzin and Gulyas[24], who mentioned the possibility that the weak effect constituted the long-wavelength tail of an intense short-wavelength broad negative band overlapped by a more narrow positive 214 nm band. (A similar explanation could not be excluded by Gacek, Undheim and Håkansson[142] in the case of the CD spectra of some α-ammonio acid amides; see below.)

Djerassi and coworkers[111] reinterpreted the lactic acid CD on the basis of their results from investigations on ethyl lactate and *O*-ethyl derivatives of the acid and the ester. The two bands were apparent in all compounds, and they exhibited solvent and temperature dependence. At liquid nitrogen temperatures only the positive short-wavelength band was present. These properties were found to be consistent with a common $n \rightarrow \pi^*$ origin of the two bands, arising from different rotamers, and in reality much less separated than shown by the spectra.

The CD spectra of the aliphatic amino acids at various pHs were reexamined by Toniolo[135]. It was found that the amino acids at pH 1 and their ester hydrochlorides in water exhibit two Cotton effects of opposite signs, centred at 206–209 nm and 244–252 nm, respectively. Results on the zwitterionic form at pH 7 confirmed previous findings that protonated amino groups[148] and carboxylate anions[111,139] do not show long-wavelength CD bands (230–270 nm). At pH 13 a weak band near 250 nm was observed, which was ascribed to the $n \rightarrow \sigma^*$ transition of the amino chromophore; (*S*)-alaninol exhibits a positive CD band at 235 nm which disappears on protonation[135]. The 240 nm band at pH 1 was ascribed to a carboxylic $n \rightarrow \pi^*$ transition.

Craig and Pereira[137] investigated the ORD and CD spectra of some α-amino and α-hydroxy acids with long-wavelength weak negative CD bands (Table 3). In their interpretation, the two bands originate from an equilibrium of conformers similar to **54** and **57**, and the additional weak band was proposed to arise from **54**, in which coupling with the carbonyl chromophore of one of the non-bonded orbitals on the α-substituent might occur. Rotamer **57** was considered to be the more favoured one. The greater nucleophilic character of nitrogen compared to oxygen should be responsible for the appearance of the weak band even in alkaline solutions in the case of amino acids, but not hydroxy acids. The absence of the band in β-hydroxy acids was taken as support for the coupling hypothesis.

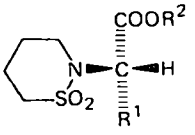
Snatzke and Doss[136] explained the chiroptical properties of amino acid sultam derivatives in terms of a conformational equilibrium of **54**–**56**, of which **55** and **56** were mainly discussed. The amino esters and corresponding ω-chloroalkyl sulphonamides exhibit a positive 210 nm band much stronger than the 240 nm

TABLE 3. CD data of some (*S*)-α-hydroxy and (*S*)-α-amino acids[a]

Compound[b]	Band 1		Band 2	
	λ_{max}, nm	$[\theta]$	λ_{max}, nm	$[\theta]$
(+)Lactic acid	210	2727	244	−17.6
(+)Lactic acid[c]	212	2157	246	−17.4
(+)Lactic acid[d]	214	744		0
(−)Calcium lactate[e]	215	432		0
(+)Glyceric acid	210	1834	244	−37.3
(+)Malic acid	212	2600	246	−47.0
(−)β-(5-Imidazolyl)lactic acid	214	2100	247	−27
(−)Methyl lactate	211	2545	240	−66
(−)Methyl α-methoxysuccinate	216	2230	242	−219
(−)*n*-Butyl α-methoxypropionate	212	1736	237	−342
(+)α-Methylbutyric acid	212	267		0
(+)Butyl β-hydroxyisobutyrate	215	192		0
(+)Alanine[g]	209	1277		0
(+)Alanine[h]	211	1261	235	−28
(+)Alanine methyl ester[j]	209	3227	236	−395
(+)Alanine methyl ester hydrochloride	208	2987		0
(−)Proline methyl ester[k]	209	2889	232	−604
(−)Proline methyl ester hydrochloride	208	3148		0
(−)*N*-Methylproline methyl ester[l]	209	1891	226	−643
(−)*N*-Methylproline methyl ester hydrochloride	209	1722		0

[a] After J. C. Craig and W. E. Pereira, Jr., *Tetrahedron*, 26 3457 (1970). Reproduced by permission of Pergamon Press Ltd.
[b] In 95% ethanol unless otherwise indicated.
[c] In water at pH 1.
[d] In water at pH 9; $\pi \rightarrow \pi^*$ 190 nm[f] (−3160).
[e] In water at pH 10; $\pi \rightarrow \pi^*$ 198 nm[f] (−3030).
[f] Lowest wavelength recorded.
[g] In 50% ethanol at pH 1.
[h] In 50% ethanol at pH 11.
[j] Amine $n \rightarrow \sigma^*$ 199 nm[m] (3564).
[k] Amine $n \rightarrow \sigma^*$ 202 nm[m] (3788).
[l] Amine $n \rightarrow \sigma^*$ 199 nm[m] (3593).
[m] Absent in the hydrochloride.

band. [Ring-closure of the latter compounds gave five- or six-membered ring sultams (59).] The alkylsulphonyl groups have no absorption bands in the



(59)

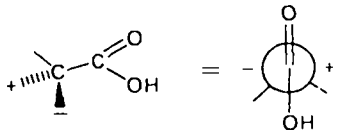
200–250 nm region (cf. Polonski[149] below). In the six-membered ring sultams, the 240 nm CD band had increased in magnitude, which was taken as evidence for an increase in the population of conformer **55** due to unfavourable dipole interactions between the carboxyl —C=O and the rigid $=NSO_2$-groups in the other rotamers.

The CD spectra of α-*N*,*N*,*N*-trimethylammonium acids exhibit a single positive 210 nm band which, according to Gacek and Undheim[141], is indicative of one

preferred rotamer, namely **54**, understandable in terms of the relative bulkiness of the quaternary amino group. The *N,N*-dimethyl derivatives of alanine, valine and leucine also show one single positive CE in both acidic (near 210 nm) and alkaline (near 220) media, suggesting the existence of one dominant conformer.

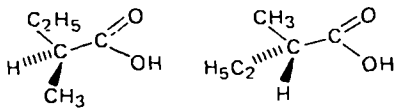
Listowsky and coworkers[127] studied the CD spectra of some L-hydroxy acids (such as the laevorotatory forms of malic acid, 2-ethoxysuccinic acid, lactic acid, and α-hydroxy-β-methylvaleric acid), L(−)-chlorosuccinic acid and D(+)-alkylsuccinic acids (ethyl, *n*-butyl, isopropyl, cyclohexyl) in aqueous solutions. The latter acids, as well as L(+)-2-methylbutyric acid, exhibit a single positive CD band near 210 nm at pH 2.5, which has changed its sign at pH 7, confirming previous ORD results of Fredga and coworkers[138]. The chiroptical properties of the hydroxy acids are compatible with the presence of two specific rotamers, **54** and **55**, of which the former as the favoured one generates the short-wavelength band. In **55** a slight overlap with a low-energy empty orbital of the α-substituent was proposed to stabilize the antibonding carbonyl orbital, lower the energy of the excited state and give the long-wavelength band. Similar explanations have been given for the red-shift observed for axial α-hydroxy, α-alkoxy and α-haloketones[151].

A simple empirical planar rule (**60a**) was proposed by Listowsky and coworkers[127], according to which in a view along the bisector of the $\widehat{OCO}$ angle as in **60b**, substituents to the left give negative contributions and those to the right



(60a) (60b)

positive contributions to the $n \rightarrow \pi^*$ CE. This rule, which gives the same result as the normal octant rule as applied to carboxylic derivatives by Snatzke and Doss[136] and by Gaffield and Galetto[155] (see below), explains why α-methylbutyric acid exhibits a single band of low intensity; **61** and **62** with a slight preference for **62**



(61) Negative CE (62) Positive CE

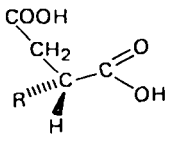
give oppositely signed contributions and no relative wavelength shifts are expected.

The empirical rule (**60a**) was used by Korver and van Gorkom[144] as a basis for the interpretation of the CD spectra of a series of 2-methyl-substituted acids and esters in terms of the rotamer distribution in various solvents and at various temperatures. In some cases, even when a single band was observed, sign inversion occurred on lowering the temperature, illustrating the importance of knowledge about the conformations involved when applying empirical rules for the determination of absolute configurations by chiroptical methods.

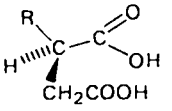
Alkylsuccinic acids were further investigated by Korver and Sjöberg[113], who observed a weak long-wavelength band even for these compounds in EPA (ether: isopertane: ethanol = 5:5:2) solution at room temperature for straight-chain alkyl groups and the isobutyl group. In the case of bulkier alkyl groups, such as isopropyl and cyclohexyl, the band was absent, and it was also absent at low temperature.

This was found to be consistent with an equilibrium between the rotamers **63** and **64**, shifted towards **63** at low temperatures and for bulky alkyl groups in accordance with the interpretation of Listowsky and coworkers[127].

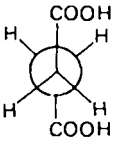
Korver and Sjöberg[113] also discuss the conformation around the $C_{(2)}-C_{(3)}$ bond on the basis of available n.m.r. data and the possibility of stabilization of rotamer **64** by intramolecular hydrogen bonds. As evidence for the latter proposal, it is pointed out that the 240 nm band was not observed for aqueous solutions[127], where hydrogen bonding with the solvent occurs, or for the dimethyl esters (except for that of methylsuccinic acid) where internal hydrogen bonding is not possible. The authors arrived at the conclusion that the *trans* form (**65**), lacking the possibility for internal hydrogen bonding, is preferred over the *gauche* form (**66**)



(63) Positive CE



(64) Negative CE



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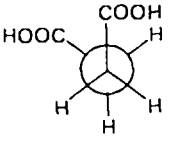


(66)

The chiroptical properties of α-substituted succinic acids and esters were also recently investigated by Craig and coworkers[152]. Their results on alkylsuccinic acids and esters confirm the observations previously made by Korver and Sjöberg[113]. In the case of the α-chloro and α-bromo compounds, an alternative[127] interpretation of their CD spectra was reached. The maximum of the short-wavelength band of the chlorosuccinic acid or ester in various solvents was found to be situated below 190 nm (for the bromo acid at 203 nm). Listowsky and coworkers[127] reported this band at 200 nm, in addition to a band of opposite sign at 222 nm, and the two bands were interpreted in terms of different conformers. Craig and coworkers[152] found that both bands increased on lowering the temperature, indicating two different transitions, which was also suggested, viz. an $n \rightarrow \pi^*$ carboxyl transition for the long-wavelength band at 222 nm (Cl) or 235 nm (Br), and an $n \rightarrow \sigma^*$ transition associated with the halogen atom for the short-wavelength band. The red-shift of the $n \rightarrow \pi^*$ transition may be explained by 'axial halogen'[151] (see above) which together with observed CD data and the application of the quadrant (octant) rule of Gaffield and Galetto[115], suggest a preferred conformation **63**. In summary, this rotamer was found predominant for α-alkyl and α-halogen compounds, whereas rotamer **64** dominated in the corresponding hydroxy-, methoxy- and aminosuccinic acids and esters.

The CD spectra of α-chloro and α-bromo alkyl carboxylic acids were extensively studied by Gaffield and Galetto[115], who observed a positive maximum at 195–222 nm for the (*S*) forms, useful for assigning the absolute configurations, and in most cases an additional negative maximum at 233–270 nm, which could be of relatively high intensity (Figure 10). These authors also proposed a conformational equilibrium of rotamers **54** (preferred) and **55** to account for the appearance of the spectra. As already mentioned, they proposed the application of the octant rule, which in principle gives the same result as the planar rule illustrated by **60a**. The rule is reminiscent of the quadrant rule for the peptide bond and may be represented by Figure 6 after exchanging nitrogen for oxygen. In the light of the recent observations of Craig and coworkers[152] on halogensuccinic acids and calculations by Richardson and Strickland[153] (see below) a reinvestigation of the α-halocarboxylic acids might be fruitful.

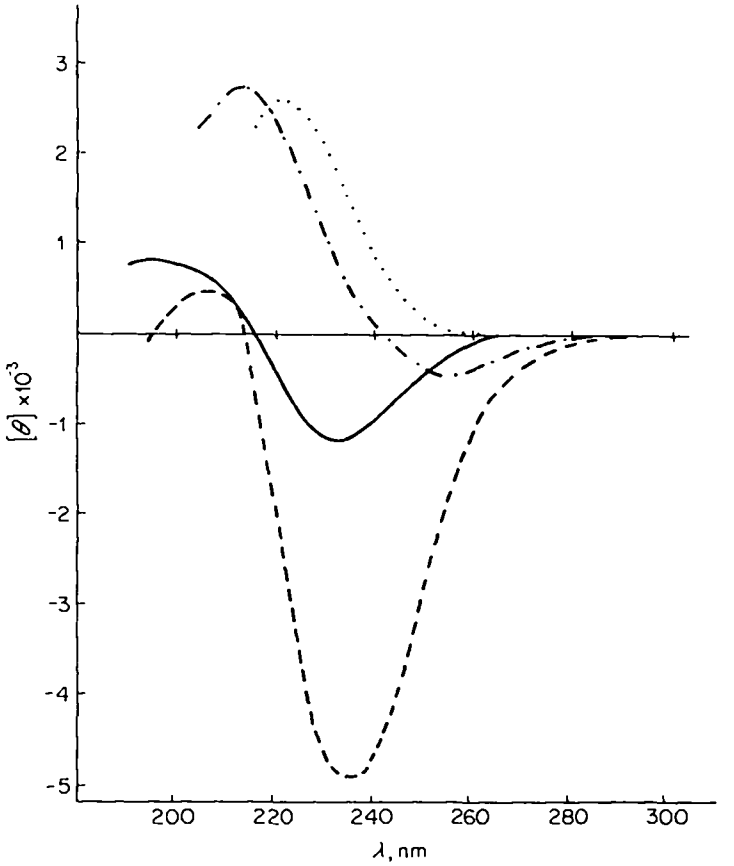


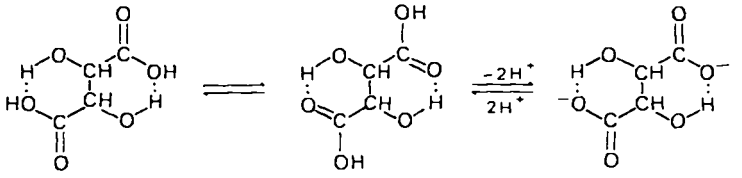
FIGURE 10. CD spectra of (*S*)-2-chloropropanoic acid (——), (*S*)-2-chloro-3,3-dimethylbutanoic acid (· · · ·), (*S*)-2-bromopropanoic acid (- - - -) and (*S*)-2-bromo-4-methylpentanoic acid (— · —) in methanol. After W. Gaffield and W. G. Galetto, *Tetrahedron*, 27, 915 (1971). Reproduced by permission of Pergamon Press Ltd.

The chiroptical properties of some α-halopropionanilides were investigated by Snatzke and coworkers[25], but in these cases the carboxylic transitions were obscured by the aromatic bands. Their discussion of the distributions of various rotamers may be of interest in this connection, however.

Scopes and coworkers[143] studied the ORD and CD spectra of (R)-2-mercaptopropionic acid and related compounds, including disulphides and derivatives containing an acetylthio or benzylthio chromophore. The *S*-alkylmercaptopropionic acids and esters exhibit a positive maximum at 238 nm, corresponding to the $n \rightarrow \sigma^*$ sulphur transition, and an additional weak band at 271 nm. The latter effect was proposed to arise from a conformer in which coupling occurs between the carboxyl chromophore and a non-bonding orbital of the heteroatom. The carboxyl CE was evident only as a shoulder at 220 nm.

The naturally occurring (+)-tartaric acid in water has a negative CD band at 216 nm shifted to 209 nm for the sodium salt[24,154]. In addition, a weak positive

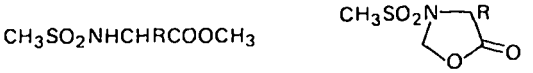
band is observed at 257 nm, which has been ascribed[154] to a bicyclic structure with internal hydrogen bonds between the carboxyl and hydroxyl groups (67). This structure was considered to be still more abundant in the dianion (68).



(67a) (67b) (68)

The problem as to whether the presence of two CD bands is indicative of two different electronic transitions or of two conformational isomers was extensively discussed by Polonski[149] on the basis of the above results and his own experiments. The absence of the weak 240 nm band in the case of α-trimethylammonio acids[141] or amino acids in the protonated form, and the shift of the band to 270 nm in the spectra of the α-mercapto acids[143], was taken as evidence that the lone-pair electrons on the heterosubstituents are involved in the transition. In Polonski's hypothesis, the 240 nm band can be assigned as an intramolecular charge transfer (CT) transition of an electron from a non-bonding orbital of the heteroatom at the chiral centre to the antibonding π^* orbital of the carboxyl group.

Supporting evidence is the fact that **69**, as well as its ring-closed form (**70**), exhibits the weak long-wavelength band in addition to a stronger one at shorter wavelengths. Structure **70** corresponds to the locked antiperiplanar rotamer (**57**),



(69) (70)

and for obvious reasons a conformational equilibrium of the kind discussed previously is excluded in this case. The observed variation in magnitude of the 240 nm band with substituent (Table 4) was explained in terms of the nucleophilicity of the heteroatom. For example, the hydroxylamine group, giving rise to a relatively strong long-wavelength band, is considered as a supernucleophile.

Evidence against Polonski's hypothesis is the fact that 2-alkylsuccinic acids and 2,3-dimethylsuccinic acid exhibit the 240 nm CD band[113;152]. Since the latter compound shows two CD bands of opposite signs it is not likely that these arise from one $n \rightarrow \pi^*$ transition in each carboxyl group (the two equivalent chiral centres have the same chirality symbol), which might be an argument in the case of the monosubstituted dicarboxylic acids. It is known (see Section IV.B.1) that in some cases sign inversion of a CD band may occur on moving the chiral centre one atom away from the chromophore.

Recently some α-amino, α-*N*,*N*-dimethylamino and α-*N*,*N*,*N*-trimethylammonio tertiary amides have been investigated by Gacek, Undheim and Håkansson[142] in order to obtain more detailed information about the two CD bands discussed. As mentioned above, trimethylammonio acids exhibit a single positive CE at 215 nm[141]. In the quaternary amino compounds, as pointed out above, no non-bonded electrons are present on the α-heterosubstituent. In the tertiary amides a different rotamer distribution and expected wavelength shifts of the CD bands (Section II) might reveal the presence of long-wavelength bands even in these cases. The α-trimethylammonio tertiary amides derived from (*S*)-amino acids exhibit a

positive CD band at 205–210 nm ($[\theta]$ ca 10^4), probably associated with the $\pi \rightarrow \pi^*$ transition, a negative band at 230–240 nm ($[\theta]$ ca 2×10^3), probably of $n \rightarrow \pi^*$ origin (see Section II), and in addition a weak positive band at 260 nm. As mentioned above, the appearance of the spectra cannot exclude the possibility that the 260 nm band is the long-wavelength tail of the 210 nm band, overlapped by a less intense and narrower 230 nm band of the opposite sign, and therefore little information was obtained.

Recently, Richardson and Strickland[153] have examined the conformational dependence of the chiroptical properties of α-hydroxy, α-fluoro, α-chloro and α-mercapto propionic acids using INDO and CNDO MO models. Rotamers **54**–**56** were considered, and in each rotamer the O–H or S–H bond was assumed to be directed on the one hand towards, on the other away from, the carboxyl group. The calculations strongly support the hypothesis that the long-wavelength band of lactic acid can be attributed to rotamer **55** and the short-wavelength band to rotamer **54**. The results for α-chloropropionic acid were in direct conflict with the suggestions of Gaffield and Galetto[115]. Better agreement with experimental data is obtained if rotamer **55** and not **54** is considered as the predominant one (which the calculations also predict), giving rise to the positive short-wavelength CE for the (*S*) form. (In conflict with rule **60b**, the calculations predict a positive CE for the $n \rightarrow \pi^*$ transition in rotamer **55** of (*S*)-α-chloropropionic acid.) An alternative explanation of the long-wavelength band is two nearly degenerate transitions, one localized on the chloro atom and one involving Cl → COOH charge transfer, which supports the hypothesis of Polonski[149]. In the case of α-mercaptopropionic acid, partial agreement between the theoretical and experimental results was found.

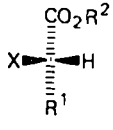
Some further examples of the presence of long-wavelength bands are given in following sections. It should be recalled that such bands were also observed in some lactone CD spectra (Section III.A.2.d).

c. Amino acids. The carboxylate sector rule of Jorgensen. Amino acids were in part discussed in the previous section. In this section some additional chiroptical properties will be pointed out. It is well known that amino acids have a zwitterionic form at intermediate pHs. As mentioned in Section III, the carboxylate anion has C_{2v} symmetry with equivalent C–O bonds. (The anhydride and imide chromophores also have relatively high symmetry, but scant CD data are available[21,155].) Consequently, the lactone sector rule of Klyne and coworkers (Section III.A.1.a), which is based on such an assumption, might well be adapted to the carboxylate anion, which was realized by Jorgensen[156]. Assuming a conformation in which the amino nitrogen lies in the $C_{(\alpha)}COO$ plane (**54**), this rule can explain the increase in the positive $n \rightarrow \pi^*$ CE with increasing bulk of the side-chain, observed for aliphatic L-α-amino acids[16], and rationalize the low optical rotation[145,157] and molecular ellipticity[30] of L-proline, as well as the negative rotation of L-azetidine carboxylic acid[158].

The discussion by Richardson and coworkers[159] of this amino acid sector rule differs in several aspects from the original description, although the essential features have been retained. These authors compare their calculated rotational strengths for various structures and rotamers of L-alanine with experimental CD spectra and with the predictions based on sector rules.

The vacuum ultraviolet CD and isotropic absorption spectra for five alkyl amino acids (Ala, Val, Ile, Leu, Pro) as zwitterions in hexafluoroisopropanol (HFIP) have been measured to 160 nm (Figure 11), and the results correlated with theoretical calculations[16]. The $n \rightarrow \pi^*$ positive CD band of the carboxylate anion is observed near 190 nm. Proline, which exhibits a sigmoidal curve between 180 and 220 nm is

TABLE 4. CD data of some carboxylic esters[a]



X	R^1	R^2	Solvent[b]	Band 1		Band 2	
				λ_{max}, nm	$[\theta]$	λ_{max}, nm	$[\theta]$
NH_2	Me	Me	m	209	+3160	227	−860
			H	207	+3060		0
			d	205	+3300	232	−720
NH_2	Me_2CHCH_2	Me	m	208	+3620	232	−1130
			H	205	+3450		0
			c	205	+6000	237	−188
NH_2	Me_2CHCH_2	*t*-Bu	m	210	+3070	235	−2150
			c	210	+6150	245	−108
NHOH	Me_2CHCH_2	Me	m	211	+4290	234	−3650
			H	209	+5100		0
			c	209	+6100		0
NH_2	Me_2CH	Me	m	210	+4300	235	−890
			H	206	+5090		0
			c	205	+8600	243	−65

NHOH	Me_2CH	Me	m	212	+5500	233	−3900
			H	205	+4600		0
			c	205	+6200	low negative	
NH_2	$MeO_2CCH_2CH_2$	Me	m	210	+2640	232	−900
			H	212	+3330		0
			c	209	+5100	235	−340
NH_2	$C_6H_5CH_2$	Me	m	210	+9000	235	−1300
			H	212	+10100		0[c]
NHOH	$C_6H_5CH_2$	Me	m	212	+8700	235	−1740
			H	210	+10600		0[d]
CH_3SO_2NH (69)	Me_2CHCH_2	Me	m	206	+4600	237	−64
			d	205	+5900	241	−20
CH_3CONH	Me_2CHCH_2	Me	m	209	+10700	240	−59
HO	Me_2CHCH_2	Me	m	209	+3800	238	−36
			c	203	+6100	240	−15
Cl	Me_2CHCH_2	Me	m	203	+2020	232	−530
			c	204	+1700	230	−1090
Compound (70)	R = Me_2CHCH_2		m	212	+2420	238	−56
			d	212	+1300	263	−200

[a] Taken from T. Polonski, *Tetrahedron*, **31**, 347 (1975). Reproduced by permission of Pergamon Press Ltd.
[b] Solvents: m = methanol, c = cyclohexane, d = cyclohexane:dioxane (9:1), H = methanol pH 1.
[c] +430 at 257 nm (^1L_b).
[d] +71 at 255 nm (^1L_b).

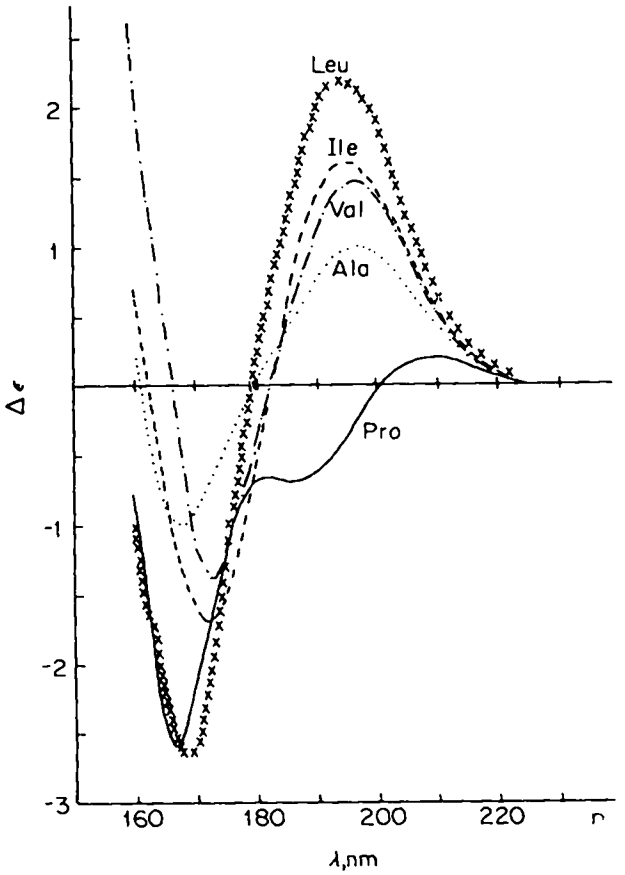


FIGURE 11. CD spectra of proline (——), alanine (• • • •), valine (— • —), isoleucine (- - -) and leucine (x x x) in hexafluoroisopropanol (zwitterions). Taken from P. A. Snyder, P. M. Vipond and W. C. Johnson, Jr., *Biopolymers*, 12, 975 (1973). Reproduced by permission of John Wiley & Sons Inc.

an exception. The $\pi \rightarrow \pi^*$ negative CD band is situated at 168–172 nm. In the alanine isotropic absorption spectrum the maximum is at 166 nm. The calculated CD signs, but not the magnitudes, were found quite reliable, again except for proline. The bisignate curve could not be explained on assuming either a conformational equilibrium, or the presence of an $n \rightarrow \sigma^*$ transition band near 190 nm. As one possible explanation, the effect of vibrational contributions to the CD was suggested, originally explored in the general case by Weigang and coworkers[160,161]. (Vacuum ultraviolet CD has also been recorded for oligopeptides and polypeptides; see next section.)

In the CD spectra of the aromatic amino acids such as phenylalanine, tyrosine and tryptophane, overlap of the rather weak carboxylic transition by the relatively strong ^1L_a aromatic transition makes the interpretation of the spectra difficult (Section IV.B.1). The absorptions of the sulphide chromophore in the sulphur-containing amino acids (disulphide chromophore in cystine[165]) also overlap with

the carboxylic one, but in this case successful separation of the various bands was possible[162,150] from their pH and temperature dependence. The members of the L-series are characterized by two positive bands, one at 198–200 nm, ascribed to the carboxyl $n \rightarrow \pi^*$ transition, and one at 215–225 nm, probably associated with a sulphur $n \rightarrow \sigma^*$ transition[163,164]. Sulphur absorption bands are also expected (from work on sulphides[163,164]) at 195–200 nm, near 210 nm and at 235–250 nm. In the spectra of L-lanthionine at medium pHs, very weak negative CD bands (maybe tails) were observed near 265 nm, and the presence of a negative CD band at 210 nm could be traced in the spectra of L-allocystathionine[162].

The CD spectra of L-cystine and some of its derivatives exhibit positive $n \rightarrow \pi^*$ carboxylic bands near 220 nm, and a negative band at about 250 nm, associated with the disulphide chromophore[165]. The chiroptical properties of these compounds were discussed in terms of the rotamer distribution, indicated from n.m.r. spectra.

In the case of cyclic cystinyl tripeptides Ottnad and coworkers[166] observed a CE at 300 nm, resulting from the interaction between the disulphide group and the amide bonds. The CD spectra are dominated by the influence of the conformation of the ring.

Recently four selenium-containing amino acids were investigated and their CD spectra compared with those of the corresponding sulphur and methylene compounds[167]. Positive CEs from the carboxyl and the selenide chromophores in the region 190–250 nm correlated with the L-configuration. The selenide transitions occur at approximately 225, 210 and 195–200 nm, i.e. at about the same wavelengths as the sulphide transitions.

d. Polypeptides and oligopeptides. Although polypeptides and proteins are derived from amino acids, their chiroptical properties are specific, and the work in this field is far too comprehensive to be accounted for within the limits of this chapter. Several reviews have been written, and presentations of the subject and leading references may be found in the general books referred to in the introduction.

However, regarding the enormous importance of the carboxyl (amide) chromophore in this connection, it might be justified to give a brief presentation of the typical CD curves associated with the various conformational arrangements of polyamino acids: α-helix, β-conformation and random coil. The general shapes of these curves are shown in Figure 12. Other typical CD patterns may be obtained for example from the polyproline helices[168]. The long-wavelength bands in Figure 12 originate from the $n \rightarrow \pi^*$ transition and the short-wavelength bands from the $\pi \rightarrow \pi^*$ transition of the amide chromophore. The CD spectrum of the α-helix may require further explanation. Due to exciton coupling[51] of the electric dipole allowed $\pi \rightarrow \pi^*$ transition, a splitting into two transitions with long-axis (at ca 210 nm) and short-axis (at ca 190 nm) polarization, respectively, takes place[35,38], as mentioned in Section II. In the CD spectrum this results in a couplet of two bands of equal rotational strength and opposite signs, as observed in Figure 12. (In fact, theory[36–38] for infinitely long helices predicts a second couplet, making it four bands of $\pi \rightarrow \pi^*$ origin which should occur at 185, 189, 193 and 195 nm.)

CD measurements in the vacuum ultraviolet region have been performed on polypeptide solutions, to 167 nm for aqueous solutions of polyglutamic acid as a helix and as a coil (and also for *N*-acetyl-L-alanine-*N'*-methylamide), and to 140 nm on poly-γ-methylglutamate in hexafluoroisopropanol (*HFIP*)[14]. In the former case, a positive shoulder on the positive 190 nm band for the helix and a negative maximum for the coil were observed near 175 nm. The HFIP solution spectrum exhibits, in addition to the 175 nm shoulder, a negative maximum at 159 nm and a

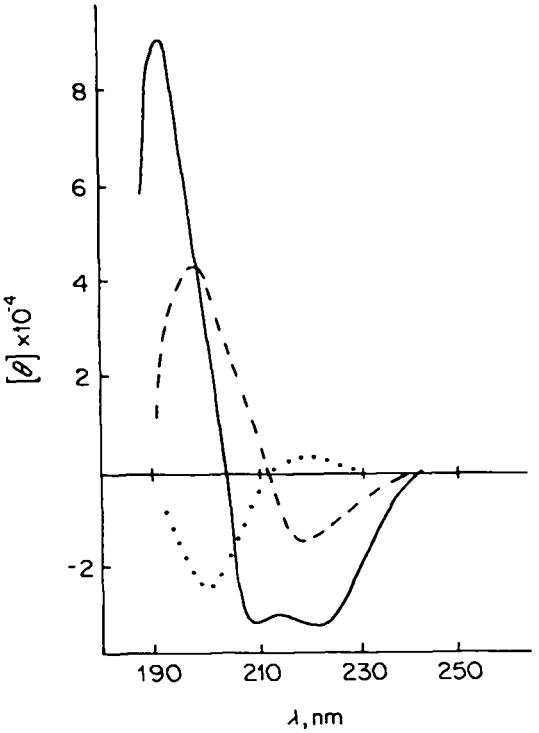


FIGURE 12. General features of the CD spectra of polypeptides in the α-helical (——), random coil (• • • •) and β-conformations (- - - -).

positive band below 140 nm. The 175 nm band was tentatively assigned to the $n \rightarrow \sigma^*$ carbonyl transition.

Quadrifoglio and Urry[169] proposed the presence of a negative 280 nm band in their resolution of the CD spectrum of helical poly-L-alanine.

In addition to the above short presentation of polypeptide CD, some interesting features of the CD spectra of oligopeptides and the related *N*-acyl derivatives of amino acids will be briefly commented on in this section. These units are also building blocks of the polypeptides, proteins, and supramolecules such as cell membranes, and by studying the chiroptical properties of the small molecules the interpretation of those of the large ones may be facilitated. Valuable information may be obtained on conformational preferences in a certain amino acid sequence. For example, residues 35–38 of α-chymotrypsin, Asp–Lys–Thr–Gly, appear as a bend, and by studying this along with three more of the 24 sequence permutations of the four amino acids, and comparing spectroscopic (CD, n.m.r.) evidence with predictions of bend conformations, more detailed information about the tendency towards forming such conformations was obtained by Scheraga and coworkers[170].

As another example, Toniolo and Bonora[171] studied the CD of the series BOC–(L-Val)$_n$–OCH_3, $n = 2–7$ (BOC = *t*-butoxycarbonyl). They observed a dramatic change in the CD spectrum on going from the hexamer (or lower members) to the heptamer. The spectrum of the latter is very similar to those reported for oligo- and polypeptides in the β-conformation (Figure 12), and this

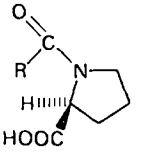
may be taken as a demonstration that the β-structure, like α-helix formation, has a critical chain length. Similar investigations were performed on the corresponding alanine and norvaline oligopeptides[172]. Vacuum ultraviolet CD spectra, recorded to 140 nm on films of the oligopeptides, revealed a substantial amount of β-conformation of the trimer in the alanine series and the hexamer in the norvaline series.

An ordered structure, such as a largely helical conformation in solution, has also been revealed by chiroptical methods for polyesters, for example for poly(β-hydroxybutyrate)[173-174].

Kajtár and coworkers[175] studied the CD of cyclo-γ-oligoglutamic acids and the corresponding *t*-Bu esters (2–4 amino acids), and they identified four bands at 240–250 nm (weak negative, not present in the acidic forms), 210–220 nm (positive, absent in the dipeptides), 200–205 nm (positive) and below 195 nm (strong negative). The latter band was assigned to the $\pi \rightarrow \pi^*$ transition and the two first mentioned to the $n \rightarrow \pi^*$ amide transition in different conformers corresponding to **55** and **54**, respectively (cf. Section IV.A.1.b). The origin of the 200 nm band was however difficult to interpret. Several suggestions were considered, such as the $n \rightarrow \pi^*$ transition of the free carboxyl or ester group, the 'mystery band' of amides[15] ($n \rightarrow 3s$; cf. Section II.B), exciton splitting of the $\pi \rightarrow \pi^*$ amide bands and intermolecular association. In any case, the chiroptical properties were discussed in terms of preferred conformations of the cyclopeptides.

Several other chiroptical studies of open and cyclic oligopeptides have been made, often combined with conformational analyses[52,55,56,64,91,176-180]. Further references may be found in those cited.

N-Acyl derivatives of amino acids and their amides belong to the simplest models of peptides. The hindered internal rotation about an amide bond, often studied by the dynamic n.m.r. technique, is well known. Nishihara and coworkers[181] have used n.m.r. and CD methods to study the conformations of *N*-acyl-L-prolines. It was found that these compounds have two main rotamers, *S-cis* (**71**) and *S-trans* (**72**), of which the latter is most populated. A positive $n \rightarrow \pi^*$ CD band of the amide chromophore was evident near 230 nm and ascribed to the *S-trans* conformer. The *S-cis* rotamer was assumed to give rise to a small negative long-wavelength band, observed at 235–250 nm.



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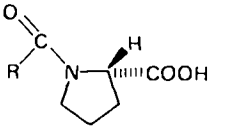

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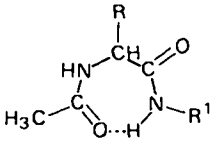
The CD spectra of acetylamino acid amides in water and in non-polar solvents have been investigated[182,183], and the solvent dependence of the $n \rightarrow \pi^*$ CE (212 nm in water, 230 nm in non-polar solvents[182]) was assumed to be conformationally related. Cann[183] studied the CD characteristics of intramolecularly hydrogen-bonded *N*-acetylamino acid amides (**73**) in *p*-dioxane. The $n \rightarrow \pi^*$ CEs of these compounds (R^1 = H) were observed at about 230 nm, whereas



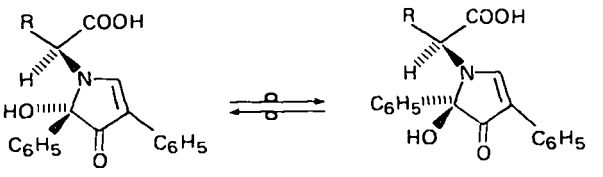
(73)

those of the intramolecularly hydrogen-bonded *N*-acetylamino acid *N'*-methylamides ($R^1 = CH_3$) and of tripeptides were centred near 220 nm (except for the corresponding proline derivative at 227 nm). The latter spectra were reminiscent of those for α-helical polypeptides, in which the corresponding CE is observed at 220–222 nm (Figure 12). It has been pointed out[20,184-185] that the α-helix provides an essentially non-polar environment for the *n* electrons of the amide group, which are completely shielded from the solvents by nestling in the cylindrical core of atoms. A similar decrease in solvent interaction with the *n* electrons may be the result of the steric conditions in the internally hydrogen-bonded *N*-acetylamino acid *N'*-methylamides.

e. N-*Substituted derivatives of amino acids.* *N*-Acyl derivatives were considered in the previous section. This section will deal with some other derivatives which have been prepared mainly to produce long-wavelength absorption. It was pointed out in the introduction that before instrumentation permitted penetration to the carboxylic absorption bands, valuable information could be obtained from various derivatives absorbing at relatively long wavelengths. These included acylthioureas[186,187] and thionamides (Section IV.A.3) for carboxylic acids in general, and metal complexes (next section), thiono derivatives, *N*-nitroso derivatives, *N*-phthaloyl derivatives, dimedon derivatives, azomethines and aldimines for hydroxy and amino acids. Of these, the dithiocarbamates were considered to be most suitable for steric correlations[188], and for this chromophore a quadrant rule was subsequently formulated[189]. Early work in this field was reviewed by Sjöberg[190], and some of the facts have been collected in Table 5.

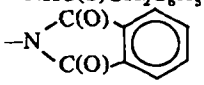
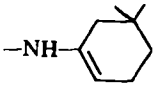
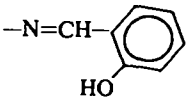
Although the carboxyl CEs are now instrumentally accessible, there is still some interest in these and similar chromophoric derivatives for various reasons, for example for the facilitation of the resolution procedure[191] or for the determination of the absolute configuration of *N*-terminal amino acids of peptides[192,193], or of newly discovered amino acids, of which several hundred have hitherto been found in nature[194-196]. The derivatives may be especially important for aromatic amino acids and for those containing another disturbing chromophore overlapping the carboxylic transitions.

The reinvestigations of previously known derivatives and the search for new ones[192,194,197-204] is often justified by some disadvantage of the former compounds, such as racemization on derivatization (phenylthiohydantoins[197]), striking solvent effects (thio derivatives[205-207]), or that the CE is not a function of the absolute configuration but remains dependent upon the nature of the α-substituent and the associated preferred conformations[194,201,202]. Among the derivatives recently investigated may be mentioned *N*-nitroso[208] and 3-hydroxypyridinium[209,210] derivatives, hydantions[204], dansylamino acids[192,203] (260 nm), *N*-methylthiocarbamoylamino acids[197] (260–265 nm), *N*-acetoacetyl amino acids[200], benzoylamino acids[199], thiobenzoylamino acids[191] (330–400 nm), *N*- and *S*-(3-nitro-2-pyridyl)amino acids[193], and *N*-substituted 3,5-diphenyl-5-hydroxy-2-pyrrolin-4-ones[194,195] (74) and (75).



(74) (75)

TABLE 5. Long-wavelength absorbing derivatives of carboxylic acids and hydroxy and amino acids[a]

Derivative	Derived from	Abs. (nm)	Sign of CE[b]
$-CONHC(S)NR_2$	$-COOH$	340	
$-C(S)NR_2$	$-COOH$	325–360	
$-NHC(S)SR$	$-NH_2$	330	Positive[c]
$-OC(S)SR$	$-OH$	355	Positive[c]
$C_6H_5-N<^{C(S)-NH}_{C(O)-CHR}$	$-NH_2$		
	$-COOH$	310	Positive[d]
$-NHC(S)C_6H_5$	$-NH_2$	365	Positive
$-NHC(S)CH_2C_6H_5$	$-NH_2$	330	Negative
	$-NH_2$	300	
	$-NH_2$	280	
$-N=C(CH_3)_2$	$-NH_2$	250	Negative
	$-NH_2$	ca 400	Negative[e]

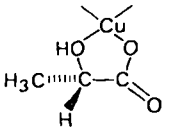
[a] After B. Sjöberg in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Ed. G. Snatzke), Heyden, London, 1967. Reproduced by permission of Heyden and Son Ltd.
[b] Refers to the L-hydroxy or L-amino acid.
[c] The L-β-amino and L-β-hydroxy derivatives[211] have negative CEs.
[d] Negative for hydroxyproline.
[e] After addition of metal.

The dimedonyl derivatives of amines and amino acids[201] are interesting since these compounds contain the vinylogous amide chromophore —C(O)-CH = C(R)NH—, which absorbs near 280 nm. The sign of the associated CE reflects the relative position of the vinylogous amide group with other chromophores in the molecule such as aromatic rings and carboxyl groups, and is thus dependent on the conformation as well as the configuration[201].

f. Metal complexes of amino and hydroxy acids. The α-amino and α-hydroxy acids form stable chelate compounds with various metals[212,213], such as cobalt[214–226], copper[190,227–234], nickel[235–238], chromium[239], zinc[146,238], vanadium[240], and molybdenum[241–243], and from their chiroptical properties the absolute configurations of the chiral acids may be deduced. The copper complexes have been known and utilized for steric correlations for a long time[190,244,245], in part depending on the easily available absorption band at 750–625 nm (sensitive to the pH). Although cobalt complexes have been used, for example for the determination of optical purity of amino acids[218,219], most of the recent research in the field of metal complexes has been focused on the metal atom–stability constants, stereochemistry of the whole complexes and transitions in the metal atoms. As exceptions, the molybdate complexes and some studies of histidine and lactic acid complexes devoted to carboxylic transitions may be mentioned[146,238].

The chiroptical properties of the molybdate complexes of α-hydroxy acids were first investigated by Voelter, Djerassi and coworkers[241], who showed that the CD spectra correlated with the absolute configuration of the hydroxy acids. Members of the L-series exhibit a negative CD band at about 260 nm and a positive CE near 210 nm. The shapes of the curves are sensitive to the pH of the solution[241,242] but the absence or presence of phenyl groups appears to be of minor importance[241,243]. As the pH changes the negative broad long-wavelength band may be divided by an overlapping narrow positive band near 250 nm. Brandänge and coworkers have demonstrated the usefulness of the CD spectra of the molybdate complexes of 2-alkylamalic acids[242] and 2-alkyltartaric acids[243] for the steric correlation of these compounds. The configurationally related free acids often exhibit CEs of opposite signs.

Urry and Eyring[146] have discussed the ORD effects associated with the carboxyl $n \rightarrow \pi^*$ transition of L-histidine in chelation with the transition metals Cu(II), Co(II), Ni(II) and Zn(II). The CD spectra of the corresponding lactates have been discussed by Bolard and Chottard[238]. They observed a negative CD band at 205–210 nm, i.e. the sign of this effect, which was ascribed to the carboxyl $n \rightarrow \pi^*$ transition, is opposite in the chelate compared to the free acid. However, the observation is in accordance with the expected signs for the rotamer (**54**) assumed for the free acid (Section IV.A.1.a), and rotamer **57** (=**76**) found for the copper complex[246].

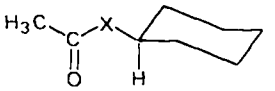


(76)

2. *Acyl derivatives of optically active amines, alcohols and thiols*

Acylation of optically active amines, alcohols and thiols results in the creation of an amide, ester or acylthio chromophore, the chiroptical properties of which may reflect the chirality of the parent compound. Primary amines and alcohols are themselves virtually transparent, even with modern instruments, scanning to 185 nm. In addition to the acyl derivatives, benzoyl derivatives are of importance for the evaluation of absolute configurations of alcohols, and diols in particular (Section IV.B.2.b).

a. Acetamides of steroids and carbohydrates. Bartlett and coworkers[247] investigated about 70 secondary acetates and acetamides derived from steroids. The preferred conformation found from n.m.r.[248,249], i.r.[250] and X-ray[251] investigations of acetate groups connected to a cyclohexane ring is that in which the carbonyl group eclipses the bond from carbon to the secondary hydrogen (**77**).



(77) X = O, NH

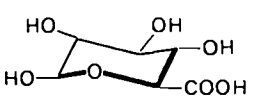
Assuming that this conformation remains in the methanolic solutions used for CD investigations and that the contributions from individual C—C bonds in the vicinity of the chromophore are additive, good agreement between predicted and experimental results was obtained.

The chiroptical properties of the acetyl derivatives have been of great value for the study of the structure and the stereochemistry of amino sugars[184,252]. Beychok and Kabat[253] investigated the ORD spectra of blood group substances, showing that mono-, oligo-, and polysaccharides containing the 2-acetamido group exhibit characteristic CEs around 210 nm. The extent and kind of substitution could be deduced, and determinations of α- or β-linkages could be made. At the same time Stone[254] made similar observations on glycosaminoglycans.

Further studies[252] revealed that all glycosaminoglycans and their component amino sugars, simple glycosides and oligosaccharides and glucoronates exhibit a negative CE near 210 nm, assigned to the amide $n \rightarrow \pi^*$ transition. A second positive band, probably associated with the $\pi \rightarrow \pi^*$ amide transition, is observed near 190 nm for 4–1 linked polymers, while those with 3–1 linked amino sugars show a second negative band below 185 nm, regardless of the presence of an α- or β-anomer configuration. Glycosaminoglycans have the component glucoronic acid (**78**) in common, but differ in their amino sugars (*N*-acetyl galactosamine, NacGal, or *N*-acetyl glucosamine, NacGlu), and in the configuration about the glycosidic bonds.

Yeh and Bush[185] have presented a theoretical treatment of the CD of *N*-acetyl amino sugars, which indicates that the sign of the $n \rightarrow \pi^*$ CE is insensitive to the anomer configuration of the sugar. Their calculations show incorrect absolute signs, but they correctly predict that the α- and β- anomers of NacGal and NacGlu have $n \rightarrow \pi^*$ CD bands of the same sign, whereas that of *N*-acetyl mannosamine has the opposite sign.

N-Acetyl neuraminic acid (NacNA) (**79**) displays a single positive band at 220 nm[252,255,256], and consequently gangleosides, which, in addition to for example NacGal, contain this component, may exhibit complex CD spectra with contributions from both components[252,255]. As seen in structure **79**, NacNa has both an amide and a carboxyl chromophore. Dickinson and Bush[256] recently studied several derivatives of NacNA and succeeded in assigning the $n \rightarrow \pi^*$ transition of the carboxyl group separately from that of the amide chromophore.



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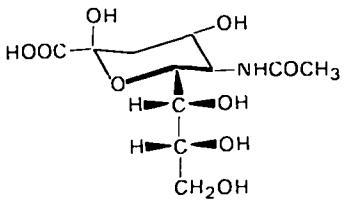
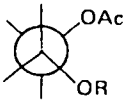


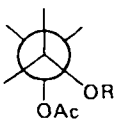
(79)

b. Acetates of carbohydrates. Acetates of steroids were mentioned in connection with the corresponding acetamides in the previous section.

Borén, Garegg and coworkers[257-259] have extensively studied the CD spectra of acetylated methyl glycosides and have succeeded in relating the sign of the $n \rightarrow \pi^*$ ester transition CD band to the molecular geometry of the acetoxy groups and their vicinal oxygen atoms. In the case of 2-*O*-acetyl and 3-*O*-acetyl derivatives of methyl α-D- and methyl β-D-hexopyranosides of galactose, glucose and mannose, the signs were empirically correlated with the dihedral angle between the acetoxy group and the bond to a vicinal oxygen atom in such a way that (**80**) gives rise to a positive CE and (**81**) to a negative CE. Thus, for the projections shown, the sign of the CE is opposite to that of the dihedral angle.

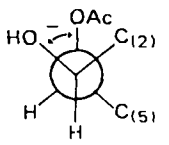


(80) Positive CE



(81) Negative CE

A similar relation holds in the case of 4- and 6-*O*-acetyl derivatives and for diacetates[259]. Predictions may be made on the assumption of additive weighted contributions from each neighbouring oxygen function to each acetoxy group[258,259]. Thus in the case of for example methyl 4-*O*-acetyl-β-D-galactopyranoside, two projections along $C_{(3)}$—$C_{(4)}$ (82) and $C_{(5)}$—$C_{(4)}$ (83),



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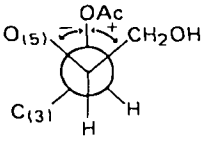


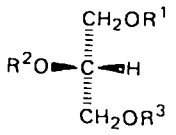
(83)

respectively, should be considered. (The signs shown refer to the contributions to the CE.) Since the influence on the CD of neighbouring oxygen functions appears to decrease in the order

$$CH_2OH \geqslant CH_2OAc \geqslant O_{(5)} > OH > OCH_3 > OAc,$$

the perturbation from CH_2OH should dominate over those from OH and $O_{(5)}$, which is in agreement with the observed positive CE[259].

c. Glycerides. Gronowitz and Herslöf[260,261] have made extensive ORD and CD investigations of mono-, di- and triglycerides (84, R^1, R^2 and R^3 = H or Acyl). A CE associated with the $n \rightarrow \pi^*$ ester transition was observed at 215–220 nm. In some cases, a solvent-dependent bisignate curve was observed, which might indicate a conformational equilibrium. This may be the case even for the relatively rigid synthetic precursors, 1,2-isopropyliden-3-acyl-sn-glycerols (85)†. However, for the



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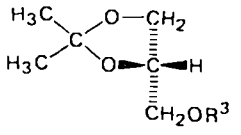


(35)

hexane solutions of these compounds, CD measurements revealed a single negative 220 nm CE, which is not observed in the ORD spectrum due to a strong positive background rotation.

3-Acyl-sn-glycerols (R^1 = R^2 = H) exhibit a positive $n \rightarrow \pi^*$ CE with highest intensity (molar ellipticities of 150–250) for ethanol solutions. The background rotation in ORD is negative.

The diglycerides exhibit strongly solvent-dependent ORD spectra, with for example positive and negative background rotations for ethanol and hexane

†'-Sn-' = stereospecifically numbered; see IUPAC–IUB rules, *Eur. J. Biochem.*, 2, 127 (1967); *Biochim. Biophys. Acta*, 152, 1 (1968).

solutions, respectively, in the case of 1,2-dimyristoyl-sn-glycerol. The $n \rightarrow \pi^*$ CE, however, is negative for both solvents, as shown by the CD spectra, and the intensity of this CE increases in ether-hexane 1:1. 1- and 3-acyl-sn-glycerols are enantiomeric, and the 2-acyl group should be of minor importance for the sign of the $n \rightarrow \pi^*$ CE, which was confirmed by the CD investigations of the di- and triglycerides. Accordingly, for mono-and diglycerides with a free terminal hydroxyl group, a positive $n \rightarrow \pi^*$ CE near 220 nm is associated with the (*R*) configuration (the sn-1-position is free).

This relationship also holds for saturated triglycerides with at least one acyl group shorter than six carbon atoms. Due to solubility problems in transparent solvents, the 220 nm CE could not be recorded for long-chain triglycerides. Since bisignate curves often occur, and one or the other of the branches may dominate, the rule may be formulated to state that the (*R*) forms (which have a longer chain in the 3-position than in the 1-position) exhibit a positive CE at 225 nm and/or eventually a negative CD band at 200 nm. Branching of the short acyl group reverses the priority in the (*R,S*) system, compared to straight-chain triglycerides, but since the sign of the $n \rightarrow \pi^*$ CE is also reversed the above relationship holds even in this case.

For the triglycerides, the background rotation and the $n \rightarrow \pi^*$ CE have the same sign, which permits the absolute configuration to be deduced from the rotation in the visible or at an accessible shorter wavelength; a positive rotation corresponds to the (*R*) configuration. Even relatively small differences in the length of the acyl groups at the 1- and 3-positions results in a detectable optical activity. For example, 1,2-dilauryl-3-myristoyl-sn-glycerol (difference two methylene groups) has $[M]^{27}_{300} = +0.8^\circ$ and 1,2-dipalmitoyl-3-myristoyl-sn-glycerol (difference also two methylene groups) has $[M]^{27}_{300} = -1.5^\circ$ in benzene, a solvent which appears to induce a high rotational value in triglycerides compared to other common organic solvents.

Unsaturation has a variable influence on the chiroptical properties, depending on its position near or far from the chromophoric ester group[261].

Work in this field is being continued and includes for example acylthio derivatives of glycerides[262] (see next section).

d. Thiolacetates. In their u.v. spectra, acylthio derivatives display an absorption band near 235 nm (ϵ ca 4000), which has been ascribed to a $\pi \rightarrow \pi^*$ carbonyl transition[94,263,264]. ORD and CD investigations of steroidal thiolacetates[264], thiepan-2-ones[94] and polymer thiol esters[94] revealed the presence of a long-wavelength CE, ascribed to the carbonyl $n \rightarrow \pi^*$ transition. Such a band, however, was not reported in the case of *S*-acetyl-(2*R*)-mercaptopropionic acid and its methyl ester[143]. In the steroidal this acetate CD spectra a positive $n \rightarrow \pi^*$ transition band was observed near 270 nm, and its intensity increased on lowering the temperature. In the ORD spectra of the polymeric thioesters and 4- or 5-methyl-thiepan-2-ones, the CE appeared to be centred around 280 nm and 298 nm, respectively.

The CD spectrum of 1,2-isopropyliden-3-thioacetyl-sn-glycerol (cf. 85) exhibits a negative CE at 265 nm and positive bands at 230 nm and 200 nm, the former one as a shoulder on the more intense 200 nm band[262]. After hydrolysis to 3-thioacetyl-sn-glycerol, the 230 nm band changes its sign to negative, making three well-resolved CD bands apparent in the 200–300 nm interval[262]. They are probably all associated with the acylthio chromophore, since the alcoholic absorption should occur at shorter wavelengths.

One octant rule[265,266] and one chirality rule[265] have been proposed for axial thiolacetates.

3. *The thionamide chromophore*

The acylthio chromophore is obtained on exchanging an ester oxygen for sulphur. Exchanging the carbonyl oxygen in an amide for sulphur (which is possible with for example phosphorus pentasulphide) creates the thionamide chromophore, which has been useful for the study of the stereochemistry of carboxylic acids and amines[1,190,267,268]. Two absorption bands, one solvent-dependent at 325 nm (methanol) to 265 nm (hydrocarbon) and ascribed to an $n \rightarrow \pi^*$ transition, and one near 265 nm ascribed to a $\pi \rightarrow \pi^*$ transition[269], give rise to two CEs in an easily accessible interval, usually without overlapping bands from other chromophores. This was utilized by Aaron and coworkers[268] to sterically correlate a series of phenylacetic acids.

Bukarevich and Djerassi[267], who studied the CD spectra of several thionamides of various kinds, pointed out the advantage of this chromophore over other derivatives used for carboxylic acids, such as acylthioureas, since the thionamide group often comes closer, sometimes adjacent, to the chiral centre. This should result in more pronounced CEs, reliable for steric correlations.

The thionamide chromophore appears to have received little interest during recent years[270].

4. *Naturally occurring complex carboxylic acids and esters*

Several of the carboxylic acids or their derivatives mentioned in the previous sections may be found in nature. However, they have been relatively simple compounds and there are numerous others, for example steroid and terpene acids[116,117,119], and compounds in which a carboxyl or ester group is part of a more complex molecule. Such compounds have recently been considered by Scopes[271] in an excellent review on the application of the chiroptical techniques to the study of natural products.

5. *α,β-Unsaturated and allenic carboxylic acids*

The chromophore present in α,β-unsaturated acids and esters[4,272] is essentially the same as in α,β-unsaturated lactones, presented in Section III.B.

The CD spectra of alkylallenecarboxylic acids and phenylallenecarboxylic acids have recently been studied by Runge and Winkler[273,274]. The allene chromophore itself gives rise to 3–4 bands in the accessible wavelength interval below 250 nm[3], and the introduction of carboxyl and phenyl groups complicates the situation. The alkylallenecarboxylic acids were analysed with the aid of CNDO/S calculations, which allowed the assignments of the various CD bands[273]. A relatively intense band near 210 nm is reminiscent of the $\pi \rightarrow \pi^*$ transition band of acrylic acid with respect to position and substituent dependence. At longer wavelengths, three weak CD bands were observed, ascribed to $\sigma \rightarrow \pi^*$ (275 nm), $n \rightarrow \pi^*$ (260 nm) and $n \rightarrow \sigma^*$ (245 nm) transitions.

B. Aromatic Compounds

In the case of aromatic carboxylic acids the carboxylic transitions are usually more or less overlapped and obscured by the aromatic ones. Most often a phenyl group is involved, and of its three bands, ^1L_b at about 260 nm, ^1L_a at about 210 nm and $^1B_{b,a}$ at about 190 nm, the two latter bands may dominate the CD

spectra. However, the assignments of CEs around 210 nm in the CD spectra of aromatic carboxylic acids have often been controversial.

It may be practical to distinguish compounds of phenylacetic acid types, in which the carboxyl and aromatic chromophores are separated by one or more atoms, and those of benzoic acid types, in which the carboxyl group is attached directly to an aromatic ring. Since the scope of this chapter is to account for the carboxylic chromophore, and not the aromatic one, just a brief description of the main features of the chiroptical properties of the compounds mentioned will be given, with attention focused on the influence on the ORD and CD spectra of the carboxylic group.

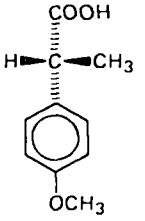
1. Phenylacetic acid types. Acid chlorides

Several investigations of the ORD and CD spectra of aromatic carboxylic acids of this kind, and their derivatives such as aromatic amino acids[38,150,209,210,275-277] and peptides[278-280] have been carried out. The studies of phenylacetic acids[112,268,281], including those of mandelic acids[147,277,282-286], in many cases give results which indicate interactions of the phenyl and carboxyl groups, giving rise to enhanced CEs from both chromophores[81,277,281]. Barth, Djerassi and coworkers[112], as well as Legrand and Viennet[287], Pirkle and Beare[288] and Fredga and coworkers[138], assigned the higher energy CE of aryl carboxylic acids at about 220 nm to the carboxyl $n \rightarrow \pi^*$ transition rather than to the phenyl ^1L_a transition, whereas other authors, for example Verbit and coworkers[282,289,290], Rosenberg[291] and Hooker and Schellman[292], are of the opposite opinion. Barth and coworkers[112] observed, in addition to the 220 nm band, a CD effect of lower intensity near 240 nm, which was ascribed to the $n \rightarrow \pi^*$ carboxyl transition of an alternative conformer (cf. Section IV.A.1.b). Craig and coworkers[281] reported two bands of the same sign in the 210–230 nm region of the CD spectra of α-alkylphenylacetic acids, which were ascribed to the benzene ^1L_a transition and to a mixed transition involving overlap of the π orbitals of the benzene ring with the $2p_y$ and π^* orbitals of the carboxyl group. (The present author, in collaboration with Fredga[293], recently reinvestigated the CD spectra of some of these compounds and observed only one single CD band in this region.) Klyne and coworkers[277] interpreted the CD spectra of some arylamino acids in terms of an enhanced carboxylic band near 220 nm and a ^1L_a transition band of the same sign at 200 nm. An alternative interpretation (using in both cases a curve resolver) involved two bands of opposite signs at 210 and 215 nm. The CD spectra of α-phenoxypropionic acids, studied by the present author in collaboration with Fredga and coworkers[293-295], exhibit, in addition to bands at 270–285 nm (^1L_b) and 200 nm ($^1B_{b,a}$), one band at 230–240 nm assigned to the red-shifted ^1L_a transition and one at 210–225 nm, which was believed to be associated with the carboxyl group. The CD spectra of the thiophene analogues of mandelic acid were recently studied by Håkansson and Gronowitz[286], and these spectra also exhibit bands near 210 nm, which might be of carboxylic origin.

In acid chlorides, the carboxylic $n \rightarrow \pi^*$ transition band is shifted to 240–250 nm (Table 1). The CD spectra of some aromatic acid chlorides were investigated by Verbit and Price[18], who identified the corresponding CD band at 250 nm, overlapping the ^1L_b CD band, but separated from the ^1L_a band CE at 210 nm. Verbit and Price point out the different widths at half-height of the carboxylic band (ca 35 nm) and the aromatic ^1L_a band (ca 20 nm). However, in the

CD spectra of α-phenoxypropionic acid chlorides[295] the chlorocarbonyl CD band could not be identified with certainty.

Although the substitution pattern of the aromatic ring may influence the CD spectra[283-285,292,296,297], chiroptical methods may be an excellent tool for steric correlations and conformational studies[285,293,298] of aryl carboxylic acids, for example the phenoxypropionic acids, which appear to be insensitive to substitution[293-295]. However, great care should be taken in comparing homologous series, since for example the sterically related 2-(*p*-anisyl)propionic acid (86) and 3-(*p*-anisyl)butanoic acid (87) exhibit CD curves which are virtually mirror



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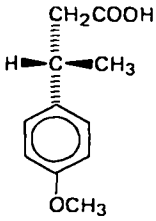


(87)

images[299]. The difference consists in a methylene group between the carboxylic group and the chiral centre, but in both cases the latter is adjacent to the aromatic ring, which most certainly gives rise to the main features of the spectra. The presence or absence of methylene groups between the chiral centre and the aromatic chromophore may also affect the signs of some CD bands. For example, the sterically related α-hydroxybenzyl- and α-hydroxyphenylacetic (mandelic) acids have ^1L_b band CEs of opposite signs at 260 nm, but 220 nm bands of the same sign, and similar relations hold for the corresponding α-amino compounds[282].

2. *Benzoic acid types*

Chiral compounds of this type include mainly the optically active biaryl carboxylic acids, possessing axial chirality like the allenic compounds, and benzoyl derivatives of optically active alcohols, diols in particular.

a. Biaryl carboxylic acids. The chiroptical properties of the biaryl carboxylic acids were first investigated by Mislow and coworkers[108] at the beginning of the sixties. Subsequently, Harris and coworkers[300,301] studied the chiroptical properties of 1,1′-binaphthyls and Håkansson and coworkers[302-307] extensively investigated the CD spectra of 3,3′-bithienyl, as well as those of some biphenyl and biselenienyl[305,308] carboxylic acids.

The CD spectra of biaryls reflect their absolute configurations, or rather conformations (helicities). A left-handed helicity (88) is associated with a relatively

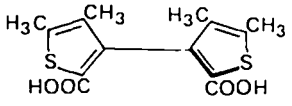

(88)

strong positive CE at 240–250 nm (for biphenyls, molar ellipticities of 10^4-10^5). However, flexible substituents, such as carboxylic groups, may have a great influence on the CD spectra. Mislow and coworkers[309] noticed that a diester, derived from a bridged and thus rigid diphenic acid, exhibited a CE near 250 nm, the sign of which was opposite to that expected for the particular absolute

configuration and conformation. Reduction of the ester groups to alcohols resulted in a reversal of the sign of the 250 nm effect. It was concluded[309] that the CE reflected the absolute twist of the ester groups relative to the aromatic rings. Similar observations have been made in the CD spectra of related bridged 3,3′-bithienyldicarboxylic acids[306,310].

Recently Siemion and Wieland[311] reported the CD spectrum associated with the helical amide – aromatic ring system, giving rise to a very strong positive CE at 235–250 nm for the right-handed helicity. This is the opposite of the helicity – sign relationship for the biaryl skeleton, which might explain the observed influence of twisted carboxylic groups. However, it is interesting that, in such a case, the result of the two opposing effects was not merely a reduction of the 250 nm band but a dominance of the carboxylic influence.

In the 3,3′-bithienyl series, the 2,2′-and the 4,4′-dicarboxylic acids exhibit rather different CD spectra (Figure 13), as illustrated by compounds **89** and **90**. The



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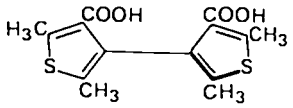


(90)

CD spectra of the former acids are relatively insensitive to solvent and ionization of the carboxylic groups, in sharp contrast to the spectra of the 4,4′-dicarboxylic acids. In some cases, such as **90**[305] the pK_1 and pK_2 values are well separated (see below), which permits investigations of the CD spectra of the acid salts, in addition to the acidic and dianionic forms. A large separation of the pK values may indicate that internal hydrogen bonds are present in the monoanions, which should keep the biaryl skeleton *as well as the carboxyl groups* in a fixed conformation.

The influence of pH on the CD spectra of **90** ($pK_1 = 4.2$ and $pK_2 = 9.0$) is shown in Figure 13. The acidic form (at pH 2.7 in 50% aqueous methanol) and the monoanion (at pH 6.2) exhibit CD curves of mirror image types, and the spectrum of the latter is reminiscent of that of **89**, though shifted towards shorter wavelengths. On going from the monoanion to the dianion, the CD band at 210–220 nm changes its sign. A similar pH dependence was observed for the biselenienyl ($\Delta pK = 5.7$) and biphenyl ($\Delta pK = 7.8$) analogues of **90**, though less pronounced for the biselenienyl. The CD spectra of two 3,3′-dicarboxylic acid esters in the solid state were also recorded[303], and the result compared to that for solution[306] and X-ray analyses[312,313].

A band associated with the carboxylic $n \rightarrow \pi^*$ transition could not be identified in the CD spectra of the biarylcarboxylic acids. (This is probably a different band to that observed by for example Mislow and coworkers and Siemon and Wieland; see above.) In the case of a 2,2′-diformyl derivative of 3,3′-bithienyl[307], a CD band exhibiting vibrational structure and probably originating from the $n \rightarrow \pi^*$ formyl transition, was observed at about 340 nm, i.e. in the range where such bands are situated in the case of α,β-unsaturated aldehydes and ketones. By analogy, the $n \rightarrow \pi^*$ carboxylic band of the compounds under consideration should be expected at 240–250 nm (Table 2), and in this region the presence of intense aromatic bands prevents the appearance of the relatively weak carboxylic $n \rightarrow \pi^*$ CD band.

b. Benzoyl derivatives. The exciton chirality method. For the determination of the absolute configurations of secondary alcohols in the form of their benzoyl derivatives, a benzoate sector rule was developed by Nakanishi and coworkers[314],

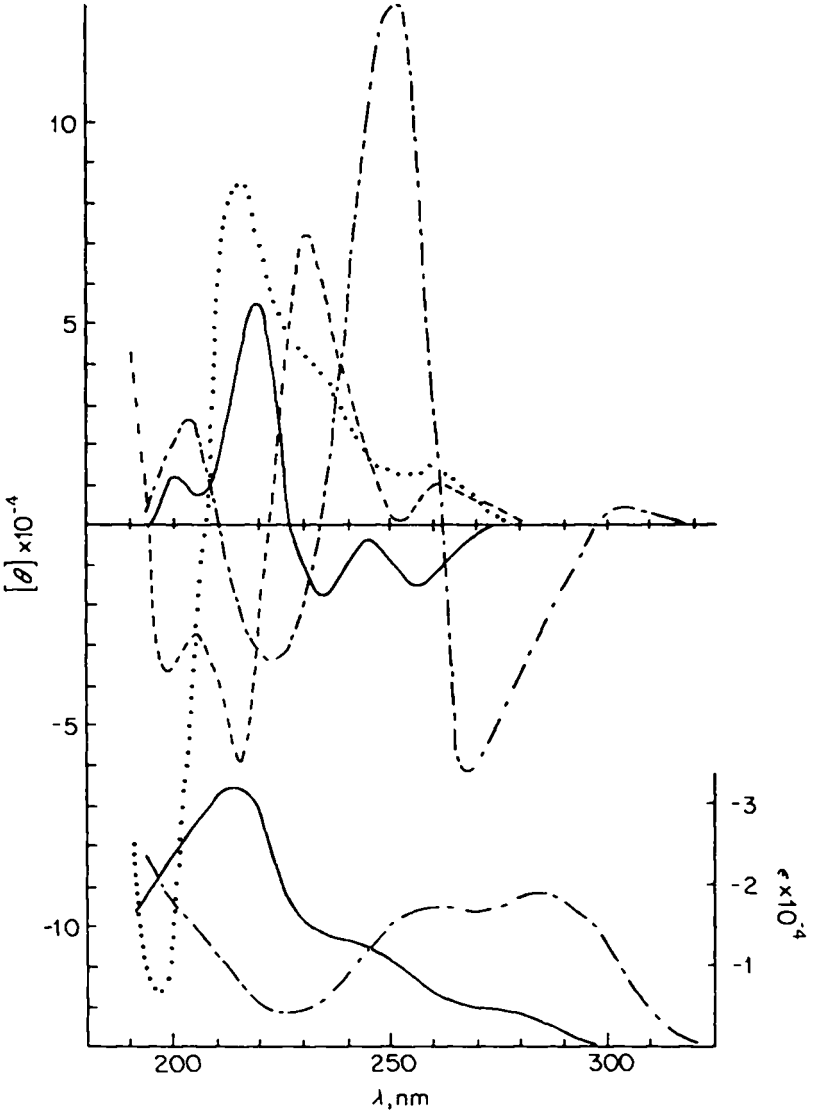
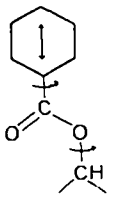


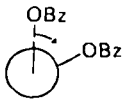
FIGURE 13. CD spectra of (*R*)-(+)-4,4',5,5'-tetramethyl-3,3'-bithienyl-2,2'-dicarboxylic acid (**89**) in ethanol (— · —) and (*R*)-(−)-2,2',5,5'-tetramethyl-3,3'-bithienyl-4,4'-dicarboxylic acid (**90**) in 50% aqueous methanol at pH 2.7 (——), pH 6.2 (- - -) and pH 11.5 (· · · ·). U.v. spectra of **89** (— · —) and **90** (—) in acetonitrile.

[315]. This was subsequently extended to the dibenzoate chirality rule, the application of which is now well known as the exciton chirality method[34]. It is applicable to 1,2-glycols on the one hand, and on the other hand also to other diols and to triols[34,316,317]. The method has been further extended to conjugated enones, esters and lactones[318].

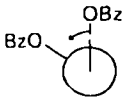
The bases for the rule are the following. Whatever the origin, the 230 nm absorption band of benzoic acid and its esters is long-axis polarized (Section II.B). Models reveal that this implies that the electric transition moment is directed parallel to the alcoholic C–O bond of the benzoate ester, irrespective of the rotations of the ester group (91). Furthermore, in dibenzoates dipole–dipole interactions of the transition moments result in a splitting into a CD couplet[51], the sign and magnitude of which reflects the dihedral angle of the dipoles, i.e. the alcoholic C–O bonds. Thus a simple chirality rule may be formulated, which is illustrated by structures 92 and 93. (It may be recalled that a couplet is a bisignate



(91)



(92) Positive couplet



(93) Negative couplet

curve, which is positive when its long-wavelength part is positive and negative when its long-wavelength part is negative.) The sign of the couplet follows that of the dihedral angle. This rule is reminiscent of the acetate rule in Section IV.A.2.b. However, the mechanisms are quite different (perturbed symmetric chromophore versus exciton coupling), and consequently also the appearance of the resulting curves and the chirality – sign relationship are different.

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER **4**

Mass spectra of acid derivatives

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I. INTRODUCTION

The basic structures of the functional groups of acid derivatives consist of the $-\overset{\overset{O}{\|}}{C}-X$ moiety where X is a radical containing either an oxygen atom or a nitrogen atom, or in the case of acyl halides, a halogen atom. The modes of fragmentation upon electron impact that are influenced either by the presence of the carbonyl function or by the heteroatom in X, or both, depend upon whether the charge is localized on one specific site or in different sites in the molecule. Fragmentations in the mass spectra may occur by simple cleavage or by routes involving skeletal rearrangements or a combination of both.

The following discussion is divided into sections according to the functional group classification. Literature on mass spectrometry according to functional groups prior to 1967 is eminently covered by the text of Budzikiewicz, Djerassi and Williams[1]. Since then, review articles on the mass spectrometry of specific organic functional groups each covering a two-year period have been published in three consecutive volumes in the *Specialist Periodic Reports* on Mass Spectrometry[2]. Other relevant texts and articles are cited in the references in these review articles[2] as well as in the biannual reviews published in *Analytical Chemistry*[3].

II. CARBOXYLIC ACIDS

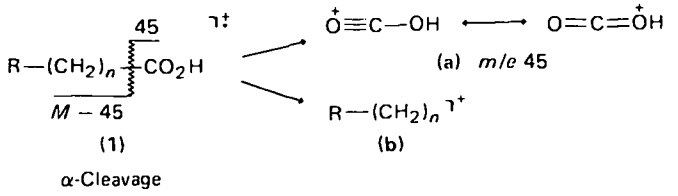
Mass spectral fragmentation studies of carboxylic acids have been relatively fewer than those of esters or amides because of the poor volatility of the samples which has often presented problems especially in the early period of the development of organic mass spectrometry. Furthermore, dehydration and pyrolytic decomposition frequently occurs at moderate temperature prior to fragmentation due to electron impact which may sometimes lead to misleading results. The problem of low volatility has largely been overcome by the use of versatile sample probes which allows the introduction of samples directly into the ion source. At the same time, by good control of ion-source temperature thermal decomposition can be avoided and what is registered in the mass spectra are true ion fragments due to electron impact. Systematic studies of the fragmentation of carboxylic acids under electron impact have increasingly appeared in the literature[1-3]. The discussion in this section is mainly focused on positive ions generated as the result of electron impact fragmentations which are characteristic of the presence of the carboxy group. Negative-ion mass spectrometry is also briefly presented.

A. Simple Aliphatic Acids

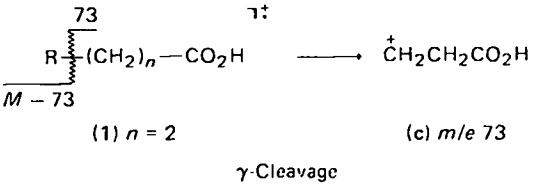
The mass spectra of lower aliphatic acids have been reported[4] in one of the earlier studies in organic mass spectrometry. Other reports[5,6] on the mass spectra of simple aliphatic acids have incorporated studies of deuterated acids.

1. Simple fragmentations

α-Cleavage of simple carboxylic acids (**1**) leads to the formation of two ions, **a** at *m/e* 45 and **b**, $[M-45]^+$. The peak at *m/e* 45 is a feature in the spectra of simple lower acids[4,5], and the appearance of $[M-CO_2H^\bullet]^+$ ions are also observed[5]. γ-Cleavage generates an ion **c** at *m/e* 73 which is also a feature of the lower acids[5].



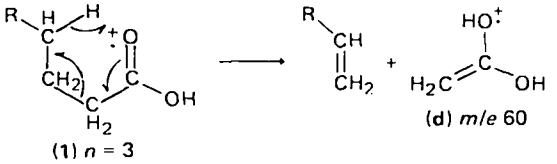
Another simple cleavage is the loss of a hydroxy group leading to the formation of the $[M - OH^{\bullet}]^{+}$ ions.



It is interesting to note that through the studies of a long series of deuterated acids and ^{18}O-labelled acetic acid, it has been established[6] that the $[M - H^{\bullet}]^{+}$ ions of $CH_3CH_2CO_2H$ and $CH_3CH_2CH_2CO_2H$ are produced not by the removal of the acidic hydrogen but exclusively by the removal of a hydrogen from the alkyl group forming ions of $[C_2H_4CO_2H]^{+}$ and $[C_3H_6CO_2H]^{+}$, respectively. For acetic acid, the $[M - H^{\bullet}]^{+}$ ion is not observed, however.

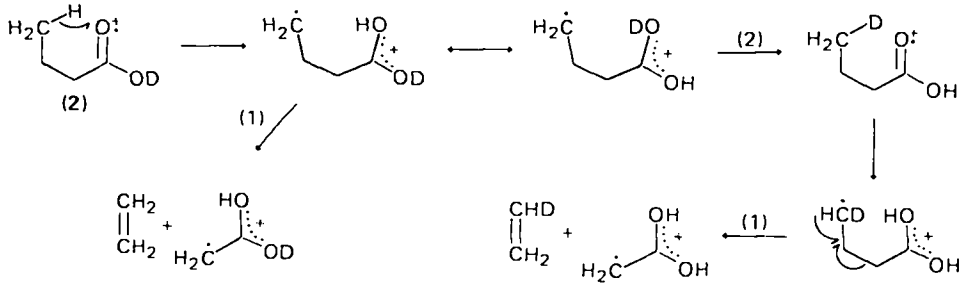
2. *Fragmentations involving rearrangements*

a. McLafferty rearrangements. One of the outstanding features in the mass spectra of simple aliphatic acids is the observation of a prominent ion, often appeared as the base peak at *m/e* 60. The genesis of this ion as a result of the McLafferty rearrangement, requires the presence of a γ-hydrogen, and its mechanism is well-documented[7].



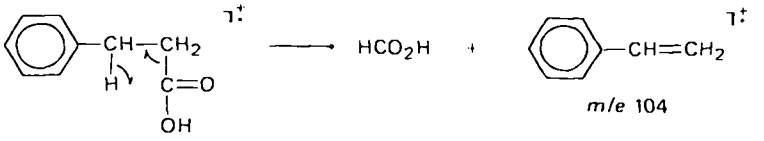
Because of this predominant formation of the McLafferty rearrangement product, simple β-cleavage is hardly observable in butyric or higher acids[4,5].

The mass spectrum of $CH_3CH_2CH_2CO_2D$ (2) shows no detectable loss of $CH_2{=}CHD$, which indicates for butyric acid either that the McLafferty rearrange-



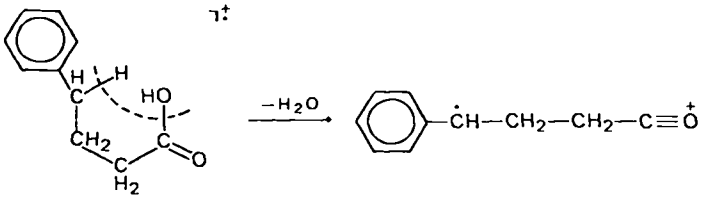
ment is concerted, or that the step involving the elimination of the olefin (*1*) is very fast in comparison to the reverse transfer (*2*) of the hydrogen back to the methylene radical[7]. Further studies on a series of deuterated butyric acids[8], including $CD_3CH_2CH_2CO_2H$ and $CD_3CH_2CH_2CO_2D$, have indicated that the McLafferty rearrangement of butyric acid indeed proceeds via a stepwise mechanism. The cleavage of the β-bond (1), which leads to the expulsion of an olefin molecule, occurs at a much faster rate relative to the αβ-C—C rotation and the reverse transfer (2) of hydrogen to the methylene radical.

b. ω-Phenylalkanoic acids. Studies of ω-phenylalkanoic acids have led to interesting observations. The major fragmentation process of 3-phenylpropionic acid (3) corresponds to the direct explusion from the molecular ion of the elements of a formic acid molecule[9]. It has been postulated[9] that the mechanism of elimination takes place via a 4-membered transition.



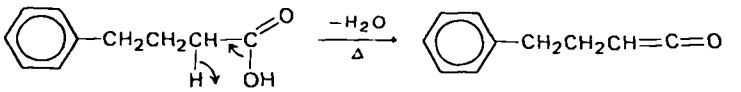
(3)

Facile loss of a water molecule from these ω-phenylalkanoic acids requires an aliphatic chain of at least four carbon atoms[10]. The elimination may occur preferentially through a 6-membered transition state, analogous to that for long-chain alcohols. This is illustrated by the elimination of H_2O from 4-phenylbutanoic acid (4).



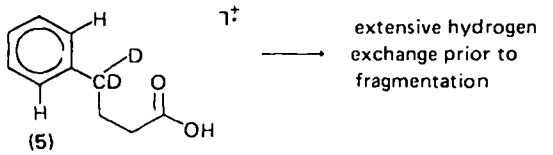
(4) (e) [*M* − 18]

Detailed studies[11] of (4) supported the above proposal, i.e. that the water molecule is expelled via a 1,4-elimination upon electron impact. In contrast, pyrolytic decomposition[11] occurs through a 1,2-elimination. It is interesting that



(4)

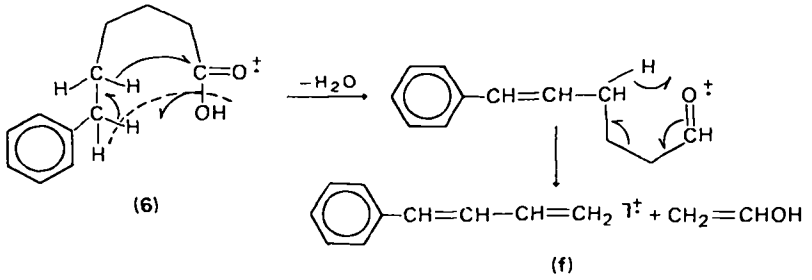
loss of H_2O and D_2O are observed in addition to the expected loss of HDO from the 4-d_2 analogue (5). It has been suggested[11] that the hydrogen atoms from



(5)

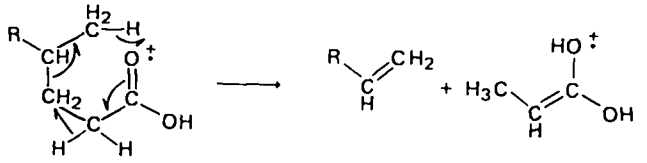
position 4, the *ortho* positions of the phenyl group, and the hydroxy group have mutually exchanged extensively prior to the water elimination.

By extending the chain to 6-phenylhexanoic acid (**6**), an abundant $[M-62]^{\ddagger}$ ion (**f**), corresponding to the combined loss of water and $CH_2{=}CHOH$, is registered in its mass spectrum[10]. A mechanism for this process has been proposed which has been confirmed by extensive deuterium labelling.



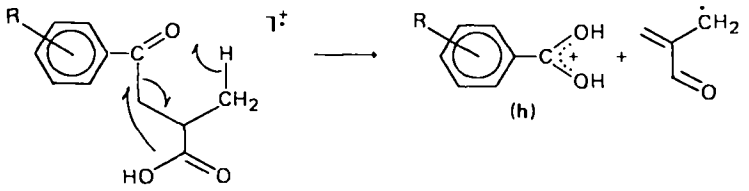
(6) (f)

c. Long-chain acids. Extension of the aliphatic chain and addition of substituents at appropriate positions along the chain may alter the fragmentation patterns of the aliphatic carboxylic acids. For example, with a methyl group substituted at the $C_{(4)}$ position, straight-chain alkanoic acids (**7**) show peaks at *m/e* 74 which may be of higher abundance than the normal McLafferty rearrangement ion at *m/e* 60. It has been suggested[12] that the ion at *m/e* 74 (**g**) may be derived from a modified McLafferty rearrangement in which a δ-hydrogen is transferred instead of the usual γ-hydrogen. A similar but less marked phenomenon has also been observed for 5-methyl and 6-methyl branched acids which shows slight enhancement for ions at *m/e* 88 and *m/e* 102, respectively.



(7) (g) *m/e* 74

Substituents at appropriate positions may govern the rearrangement processes. As an illustration, a complex rearrangement on electron impact for β-benzoyl-α-methylpropionic acids (**8**), involving both hydrogen migration, has been re-



(8) (h)

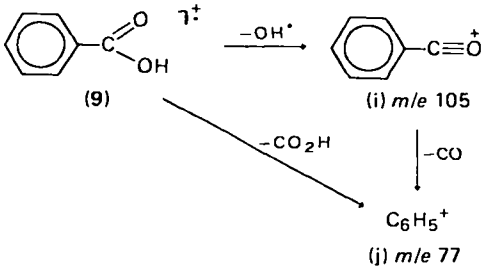
corded[13]. The rearrangement process, giving rise to an ion **h**, is favoured by electron-withdrawing substituents in the phenyl group.

B. Aromatic Acids

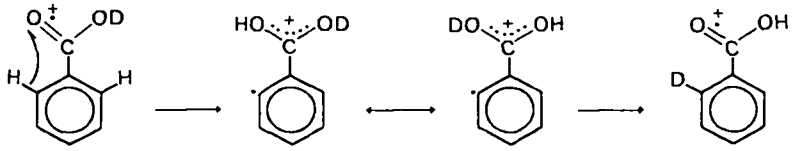
With the carboxy group attached directly to the aromatic nucleus the only simple fragmentations that are likely to occur are the cleavage of the hydroxy group and/or the carboxy group. Expulsion of a molecule of CO or CO_2 from the molecular ion would result in rearrangements. Furthermore, exchange involving the *ortho* hydrogen or substituents participating in the *ortho* effects are common phenomena in fragmentation processes due to electron impact in aromatic acids.

1. Benzoic acid

The major fragments observed in the spectrum of benzoic acid (**9**) appear at *m/e* 105 (i) and *m/e* 77 (j) due to the sequential loss of a hydroxy group and carbonyl group[14], or direct loss of a carboxy group. However, studies of the



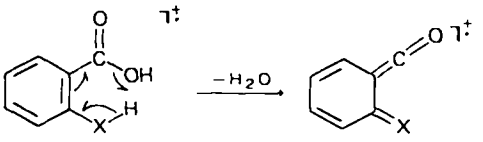
deuterated benzoic acids have revealed that the loss of the hydroxy radical is not limited to the original hydroxy group[15,16]. It has been established[17] that exchange of the *ortho* and hydroxy hydrogen atoms takes place prior to fragmentation and approximately 18% of the hydroxy group expelled from the molecular ion contains hydrogen from the *ortho* position. In another independent study[18] it has been shown that in the unlabelled acid 24% of the ions (i) have lost hydrogen from the *ortho* position.



The elimination of CO from the molecular ion of benzoic acid is rather complex. At 15 eV approximately 80% of the CO derives from the original carboxy group, and 20% of the carbon comes from the ring. Even at 70 eV, approximately 10% of the carbon comes from the ring[18].

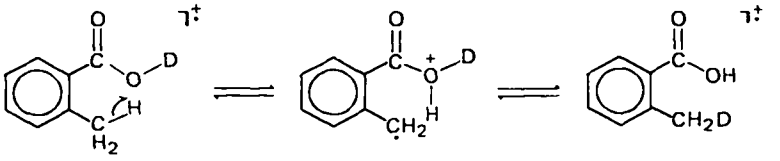
2. Substituted benzoic acids

Substituents containing an α-hydrogen atom situated at the *ortho* position to the carboxy group undergo loss of water from the molecular ion. Examples of this common phenomenon include *o*-toluic acid[19] (**10**), salicylic acids[20,21] (**11**), anthranilic acid[22] (**12**), and *o*-isopropylbenzoic acid[23] (**13**).



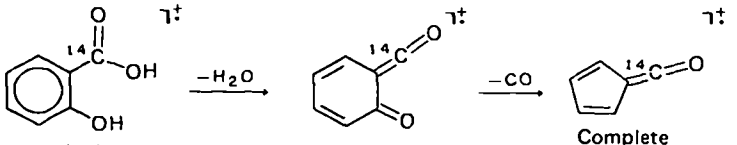
(10) X = CH_2 *m/e* 118
(11) X = O *m/e* 120
(12) X = NH *m/e* 119
(13) X = $^{*}C-CH_3$ *m/e* 131

It has been shown[19] that hydrogen exchange between the methyl group and the carboxy group in O-d_1 of (**10**) occurs prior to the loss of H_2O. There is, however, no evidence for the involvement of ring hydrogen atoms in exchange with the carboxy hydrogen as in the case of benzoic acid[17].



(10) O-d_1

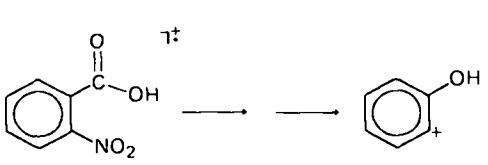
In the case of salicylic acid[21], hydrogen exchange before the formation of the $[M-18]^{+\cdot}$ ion occurs to a much lesser extent than it does in benzoic acid prior to the formation of the $[M-17]^{+}$ ion. With the carbon atom of the carboxy group labelled with ^{14}C, it has been confirmed[24] that complete retention of this carbon is observed in the subsequent expulsion of a CO molecule.



(11)

Complete retention of ^{14}C

o-Nitrobenzoic acid[14] has received much attention, and extensive labelling studies with ^{13}C and deuterium have led two schools[25,26] to suggest alternative pathways for the generation of the rearranged ion (**k**), which is unique for *o*-nitrobenzoic acid.



(14) (k) *m/e* 93

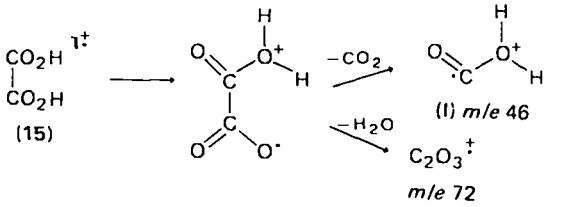
Substituents at the *ortho* position significantly influence the fragmentation of the carboxy group. Such phenomena are generally known as the '*ortho* effect' or 'proximity effect'. Substituents at the *meta* and *para* position[27] play only a minor role in exerting an effect on the fragmentation pathway of the carboxy group.

C. Dicarboxylic Acids

The mass spectra of the homologous series of acids $HO_2C-(CH_2)_n-CO_2H$ (for $n = 0$ to 12) have been studied[28]. In the lower members of the series, the carboxy–interaction plays an important part in governing their fragmentations upon electron impact. As n increases, the intramolecular effect decreases and one of the significant fragmentations is the loss of one or two molecules of H_2O which proceeds most favourably via a 6-centred intermediate involving the methylene group β to a carboxy group.

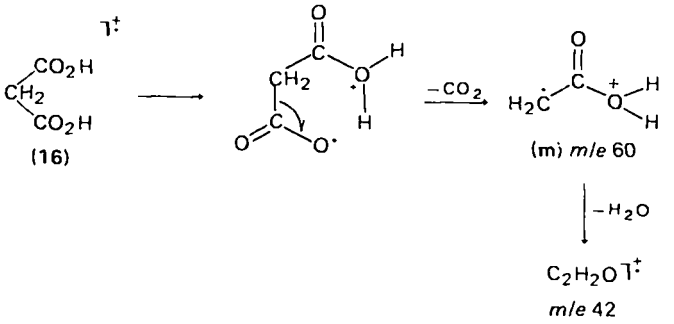
1. *Oxalic acid*

It has been observed[28] that carboxy–carboxy interaction promotes CO_2 elimination. In the case of oxalic acid (**15**) the following pathways are observed. It may be of interest to note that the ion structure and energy content of the ion I are different from those of the molecular ion of formic acid[29].

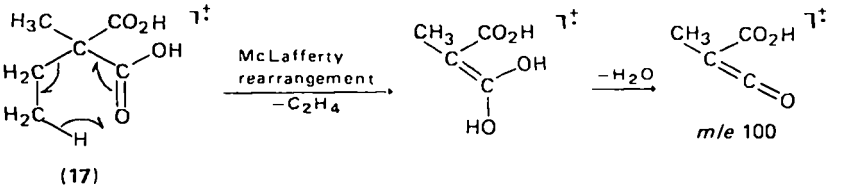


2. *Malonic acid*

Unsubstituted malonic acid (**16**) fragments upon electron impact in a manner similar to that of oxalic acid[28].



Large alkyl substituents may provide hydrogen atoms or groups that lead to other fragmentation modes[30]. For example, methylethylmalonic acid (**17**) fragments according to the following pathway:



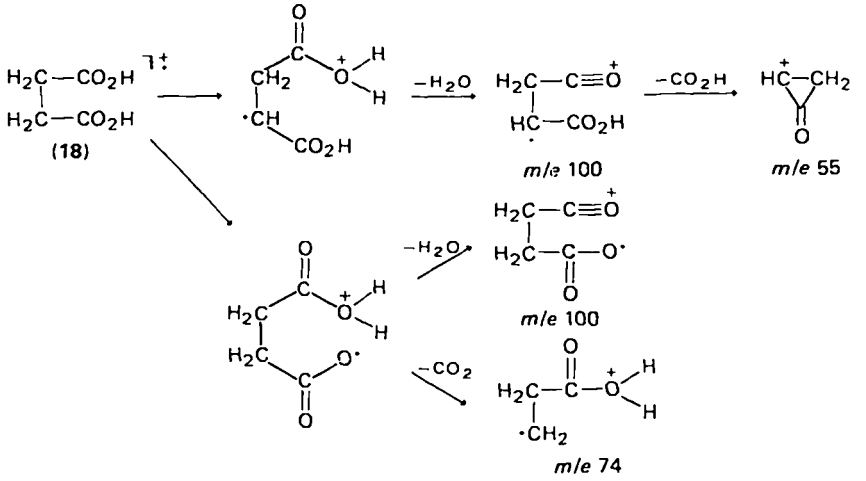
n-Butylethylmalonic acid gives a prominent $[M - 55]^+$ ion which is the result of direct elimination of the large *n*-butyl group. By increasing the size of the substituents, e.g. in the case of di-*n*-octadecylmalonic acid[30], facile loss of one of the substituent groups and/or ready occurrence of rearrangements prevent the formation of the parent molecular ion[31].

Again the ion structure and energy content of the ion m are different from that of the molecular ion of acetic acid[29]. The difference is more apparent in the case of the malonic acid–acetic acid pair than in the oxalic acid–formic acid pair[29].

3. *Succinic acid*

The initial major fragmentation of the molecular ion of succinic acid (**18**) is the loss of a H_2O molecule. Since succinic acid and other acids where the separation of the two carboxy groups is the same[32], e.g. cyclohexan-1,2-dicarboxylic acid, cyclohexene-1,2-dicarboxylic acids and phthalic acid, readily lose a molecule of H_2O thermally to form the corresponding anhydride, special care must be taken to ensure that the mass spectra registered are due solely to electron-impact fragmentations. Control of ion-source temperature is also of utmost importance.

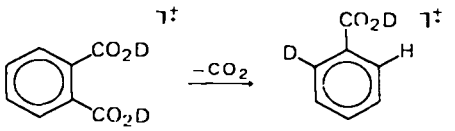
It has been established[28] that both mechanisms as illustrated below are operative in the fragmentation of succinic acid.



Molecular geometry may affect the fragmentation mode, perhaps due to the change of carboxy–carboxy interactions. It is interesting to note that the mass spectra of the *cis* and *trans* stereoisomers of cyclohex-4-ene- 1,2-dicarboxylic acids are very similar[33] whereas those of the *cis* and *trans* stereoisomers of cyclohexane-1,2-dicarboxylic acids are readily distinguishable[34].

4. *Phthalic acid*

The spectrum obtained by direct insertion of the sample probe into the ion source at a temperature of not higher than 100° shows almost no evidence of dehydration. In contrast to benzoic acid no loss of OH• is observable[16,18] from the O-d_2 phthalic acid (**19**). No *ortho* and hydroxy hydrogen exchange is evidenced. However, explusion of a CO_2 molecule from the molecular ion gives a



(19) (n) *m/e* 124

species which behaves as an ionized benzoic acid (**n**) and exchange of *ortho* and hydroxy hydrogen atoms is operative[16]. Furthermore, hydrogen-atom transfer from one carboxy group to the other is observed in the molecular ion.

5. Maleic and fumaric acids

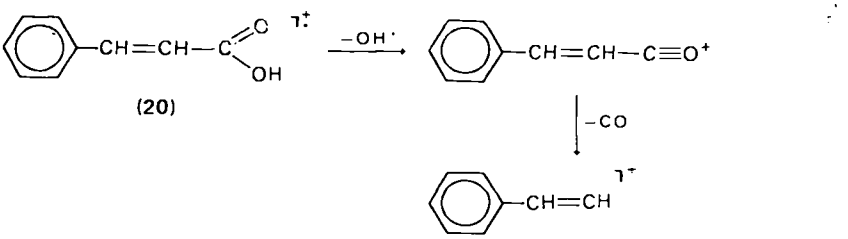
With the introduction of a double bond at $C_{(2)}$—$C_{(3)}$, the two carboxy groups occur either *cis*, as in maleic or citraconic acids, or *trans*, as in fumaric or mesaconic acids. It has been observed[35] that, in the case of *cis* acids, hydrogen-atom transfer from one carboxy group to the other occurs prior to its characteristic elimination of a CO_2 molecule followed by loss of H_2O. In the case of *trans* acids distinctively different fragmentation pathways are observed[35], e.g. fumaric acid gives major fragments of $[M - OH^{\bullet} - CO]^+$ and $[M - CO]^{+\cdot}$ ions

D. Other Acids

There are several types of carboxylic acids whose mass spectra have been studied but which cannot be placed in any of the above classes. These include the unsaturated acids, halo acids and thio acids.

1. Unsaturated acids

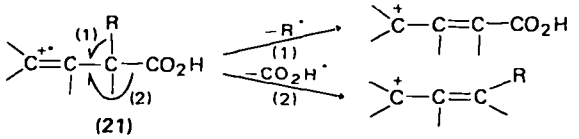
One of the unsaturated acids that has attracted some attention is cinnamic acid (**20**) whose fragmentation pathway is shown[36] to occur by the following steps:



(20) (o) *m/e* 103

The styryl ion (**o**) is formed via the stepwise fragmentation process of $[M - OH^{\bullet} - CO]$.

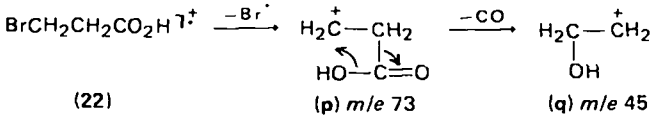
Based on the studies of a series of β,γ-unsaturated acids (**21**) it has been shown[37] that the major fragmentation routes of acyclic and cyclic acids are similar. In contrast to saturated acids, only cyclic compounds undergo McLafferty rearrangement; neither the ion a at *m/e* 45 nor γ-cleavage are observed. It is evidenced[37] that the positive charge is mainly localized on the π C=C system, thus promoting allylic cleavage which involves the competitive loss of an alkyl group (when present) and of a carboxylic acid radical.



(21)

2. Halo acids

The initial loss of a halogen radical is usually the major fragmentation from the molecular ion of α- and β-halo acids[38]. For example, the base peaks of the mass spectra of 2-chloro-, 2-bromo- and 3-bromo-propionic acids (22) are revealed at *m/e* 73, in each case due to the initial loss of a halide radical. It has also been established[38] that ion p at *m/e* 73 undergoes rearrangement giving rise to an ion (q) at *m/e* 45 which is isobaric with carboxyl ion, CO_2H^+. Exact mass measurement confirmed that the peak at *m/e* 45 is indeed a doublet consisting of two ions of the composition $C_2H_5O^+$ and CO_2H^+.

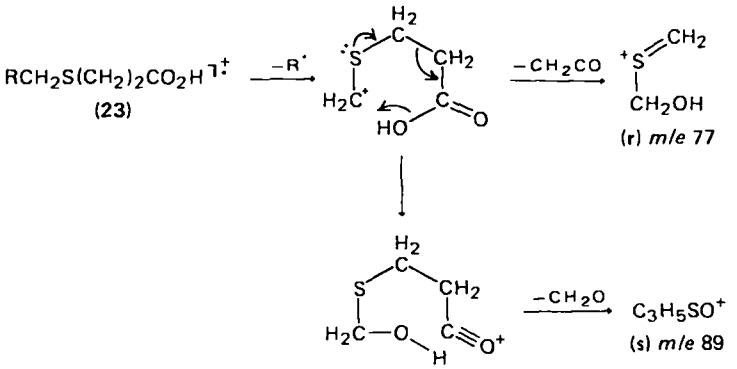


(22) (p) *m/e* 73 (q) *m/e* 45

3. Thio acids

One of the common features of sulphur-containing compounds is, in addition to simple fragmentation, the observation of extensive skeletal rearrangements upon electron impact. Detailed studies of the mass spectra of a series of thioglycollic acids[39] have revealed several interesting rearrangement processes.

β-(Alkylthio)propionic acid, $RCH_2S(CH_2)_2CO_2H$ (23), shows rearrangement ions produced by the processes $[M - R^{\bullet} - CH_2CO]$ and $[M - R^{\bullet} - CH_2O]$ giving rise to ions r at m/*e* 77 and s at *m/e* 89, respectively[40]. These rearrangements only



(23) (r) *m/e* 77 (s) *m/e* 89

occur in acids. Furthermore, the abundance of these ions increases with the size of the alkyl side-chain R.

E. Negative-Ion Mass Spectra of Carboxylic Acids

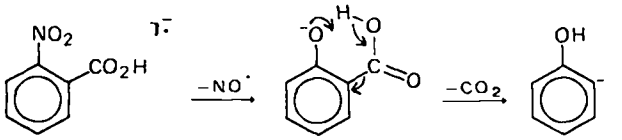
One of the earlier reports of negative-ion organic mass spectrometry includes the study of formic acid and its deuterated analogues[41]. The relative sensitivities of the

formation of negative ions of RCO_2^- from formic, acetic and propionic acids have been determined[41]. The major difficulties inherent in the production and measurement of negative ions were primarily due to the small number of negative ions produced upon electron impact and the common occurrence of ion–molecule reactions.

The absence of molecular anions is a general phenomenon in negative-ion spectra of aliphatic compounds. The negative-ion spectra of aliphatic mono-[41] and dicarboxylic acids[42,43] show prominent $[M - H^\bullet]^-$ anions. In addition, informative and abundant ions such as $[M - H_2O]^{\bullet-}$ and $[M - CO_2H^\bullet]^-$ are also observed[42] in the spectra of dicarboxylic acids. The molecular ions of phthalic acids are much more abundant than those of aliphatic dicarboxylic acids.

The base peaks in the spectra of maleic and fumaric acids[42] are revealed as $[C_2H_3]^-$ ions. Maleic acid, being in a *cis* configuration, is less stable than fumaric acid which has a *trans* geometry. It has indeed been observed[42] that the molecular anion of fumaric acid is more abundant than that of maleic acid. However, the reverse is true in the case of $[M - H^\bullet]^-$ ions for these two acids.

Other carboxylic acids that have been studied in detail include the nitrobenzoic acids[44] and the anthraquinone 1- and 2-carboxylic acids[45]. Distinctive and marked 'proximity effects' are observed in the negative-ion spectrum of *o*-nitrobenzoic acid (24) which fragments according to the sequence $[M - NO^\bullet - CO_2]$ producing the



(24) (t) *m/e* 93

anion t at *m/e* 93. On the contrary, anthraquinone 1- and 2-carboxylic acid molecular anions[45] show no substantial difference in decomposition and hence no 'proximity effect' is exerted on these two isomers. The basic fragmentations are identical and the major anions observed are $[M - CO_2H^\bullet]^-$ and $[M - CO_2]^{\bullet-}$.

III. ESTERS

Since, as mentioned in the previous section, the low volatility of carboxylic acids presents technical problems, mass spectrometric studies of acids are most conveniently carried out in the form of esters, in particular, methyl esters. In fact, because they are thermally stable and volatile, esters are the class of compounds that has been most widely and extensively studied. The discussion in this section follows the same pattern as adopted in the previous one for carboxylic acids.

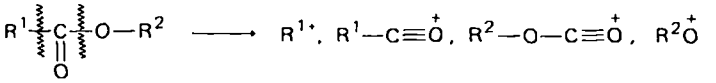
A. Aliphatic Esters

The mass spectra of simple aliphatic esters have been studied in great detail and are well-documented[46-50]. With the extensive use of deuterium labelling, exact mass measurements and metastable peak studies[51], the fragmentation modes of most simple aliphatic esters have been firmly established.

1. Simple fragmentations

For esters of $R^1-\overset{\overset{O}{\|}}{C}-O-R^2$ (25) where R^1 and R^2 are alkyl groups (except in

formates where R^1 = H), α-cleavage could theoretically yield up to four ions, **u**, **v**, **w** and **x**, although some of these may not necessarily be primary fragments from the molecular ions. Of these four possibilities, **v** and **w** are usually the more prominent ions. However, **u** is of considerable abundance especially in spectra of methyl acetate, propionate, butyrate and valerate[52].



(25) (u) (v) (w) (x)

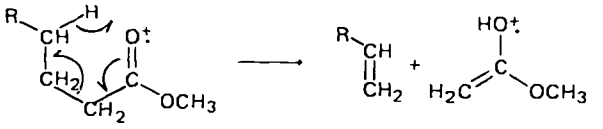
The acylium ion **v**, $R^1-C\equiv O^+$, is diagnostic and useful in the interpretation of mass spectra of simple aliphatic esters[48,49]. Its relative abundance gradually decreases with increase of the carbon chain length of R^1.

Corresponding to the γ-cleavage in carboxylic acids, fragment ions of general formula $[(CH_2)_nCO_2CH_3]^+$, where *n* is an even integer, have been observed in the spectra of normal long-chain methyl esters[53]. It has been shown that in the mass spectrum of methyl myristate, $CH_3(CH_2)_{12}CO_2CH_3$, the prominent ions include the molecular ion at *m/e* 242, $[M - OCH_3^{\bullet}]^+$ at *m/e* 211, the McLafferty rearrangement ion at *m/e* 74, and a series of $[(CH_2)_nCO_2CH_3]^+$ ions at *m/e* 87, *m/e* 143 and *m/e* 199.

In long-chain esters where there is a phenyl substituent in the non-terminal position, cleavage has been observed[54] preferentially at the branching position. Examples are given for methyl 3-, 4- and 5-phenylpentanoates and methyl phenylnonanoates. Because of the preferential fragmentation sites, mixtures of isomeric esters can be analysed qualitatively and quantitatively by mass spectrometry.

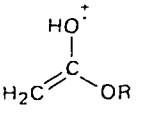
2. *Fragmentations involving rearrangements*

a. McLafferty rearrangements. As for carboxylic acids, one of the most outstanding features in the mass spectra of simple aliphatic esters is the observation of prominent ions resulting from McLafferty rearrangements. For example, in the case of methyl esters of butyric (26) or higher acids, the base peak is usually observed at *m/e* 74 corresponding to $[C_3H_6O_2]^{\ddagger}$ whose ion structure is depicted as **y**[47,49].



(26) (y) *m/e* 74

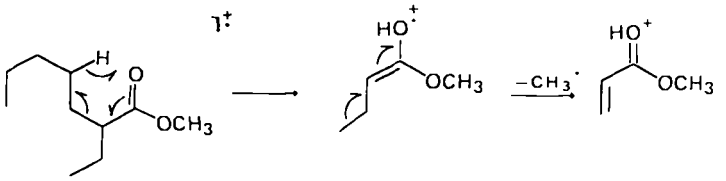
Ethyl or higher esters[55] rearrange in the same manner as methyl esters giving rise to ions of general type of $[R{-}C_2H_3O_2]^{\ddagger}$ as represented by **z**, particularly noticable at *m/e* 88 and *m/e* 102 for ethyl and propyl esters, respectively.



(z)

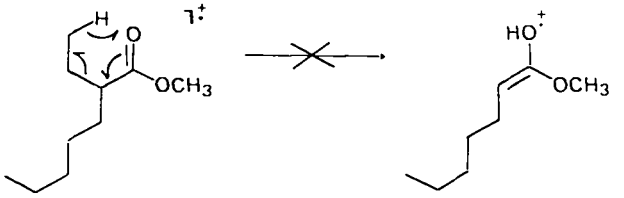
Studies of the competitive transfer of hydrogen and deuterium atoms attached to the same carbon atom at the γ-position relative to the carbonyl group in labelled esters afford the measurement of the primary 'isotope effect' (IE) which is defined[56] as 'the atoms of deuterium per atom of hydrogen transferred for the hypothetical case in which equal number of deuterium and hydrogen are available'. In the case of γ-d_1- and γ-d_2-methyl butyrates[57], a value of 0.88 was obtained for both labelled esters. For γ-d_1-methyl valerate[56], the value of 0.92 was obtained.

For compounds where there is more than one site from which a γ-hydrogen atom can be provided for McLafferty rearrangement, it has been demonstrated[58] that the larger alkyl group participates and the nature of the branching is then indicated by allylic fission of an alkyl radical. To illustrate this finding, methyl 2-ethylheptanoate (27) was found to fragment according to the following path-



(27) (aa) *m/e* 102 (ab) *m/e* 87

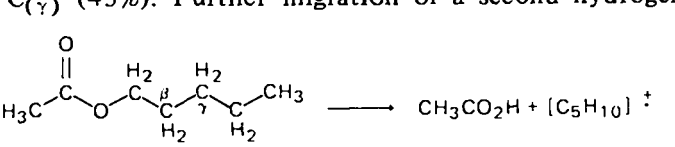
way[58] to yield ions, **aa** and **ab**. The other possible fragmentation pathway involving the migration of a γ-hydrogen of the ethyl chain is hardly observable.



(27) negligible

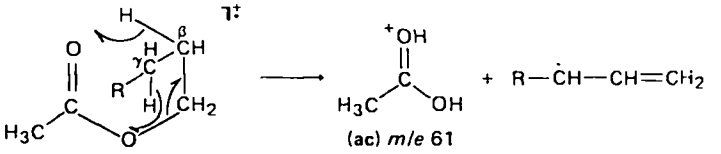
Results on the substituent effects in the mass spectra of some γ-substituted methyl butyrates[59,60] in relation to the McLafferty rearrangement have been presented. It has been shown that the substituent effect on the appearance potential of the ion at *m/e* 74 (and also the $[M-74]^+$ ion) is small, which tends to indicate that the requirement for charge stabilization at the γ-position in the transition state is little or nothing. This supports the mechanism of concerted radical transfer.

b. Hydrogen migration involving the alcohol chain. When the alkyl group attached to the oxygen atom has two or more carbon atoms, migration of one or two hydrogen atoms from the alkyl chain to the acid moiety also occurs. In a study of *n*-pentyl (28) and *n*-hexyl acetates[61], it has been shown that the transfer of one hydrogen atom according to the following equation is derived from positions $C_{(\beta)}$(55%) and $C_{(\gamma)}$ (45%). Further migration of a second hydrogen to yield a



(28)

'protonated acid' ion at *m/e* 61 (ac) for acetates is a common process[47]. It has been concluded[50,61] that the double hydrogen-atom migrations are predominantly derived from the β- and γ-positions. Whether the mechanism of transfer of the two hydrogen atoms is concerted or stepwise-occurring is a complicated problem, since scrambling of the hydrogen atoms along the chain may occur prior to or during the process of migration. Deuterium labelling at specific positions before electron impact may be completely scrambled if the time-scale for randomization of hydrogens in the molecular ion is shorter than that for hydrogen transfer. It is interesting



(ac) *m/e* 61

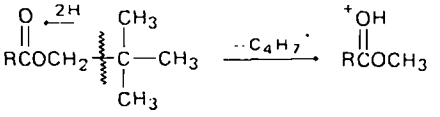
to note that almost complete scrambling of the ethoxy hydrogens in ethyl esters (**29**) occurs prior to rearrangement, whereas the source of hydrogen transfer in isopropyl esters (**30**) is predominantly derived from the methyl groups[62]. Further-

$RCOOC_2H_5$ $RCOOCH(CH_3)_2$

(29) (30)

more, it has been shown[63] that hydrogen scrambling in the molecular ion of ethyl acetate occurs via at least two different and distinct mechanisms, one involving the ethoxy hydrogens only and the other one scrambling the acetyl and ethoxy hydrogens in the molecular ions. With such vast variations from compound to compound, results based on isotopic-labelling studies should be interpreted with caution.

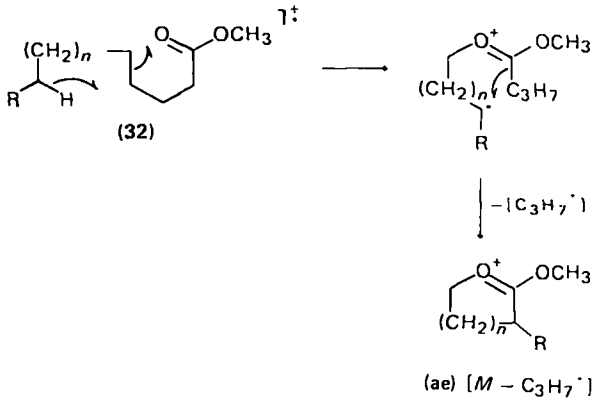
Studies of a series of neopentyl esters[64] (**31**) have revealed that prominent ions of type $[M - C_4H_7^{\bullet}]^+$ are observed in all spectra. The formation of the $[M - C_4H_7^{\bullet}]^+$ ions, which would correspond to the protonated acids, is evidently derived from the migration of two hydrogen atoms and fission of the weak C—CMe_3 bond resulting in ion structures (**ad**) formulated as protonated methyl esters[64].



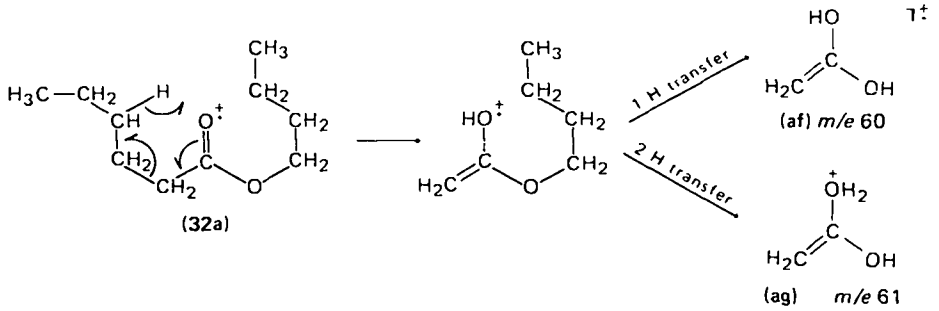
(31) (ad)

c. Long-chain esters. By extending the chain lengths of the acid end or the alcohol end, or both, competitive hydrogen migrations may occur. With the extensive use of deuterium labelling, sometimes coupled with ^{13}C labelling[65,66], it was possible to locate some of the specific rearrangement sites[65]. One example which may be of general interest is the study of methyl octadecanoate[66] (**32**) whose base peak is produced by a specific McLafferty rearrangement, but the loss of an alkyl radical may be derived from either simple cleavage at the end of the chain or through a complex internal rearrangement as depicted below, giving rise to ion **ae**.

The processes in forming ions at *m/e* 60 (**af**) and *m/e* 61 (**ag**) from esters where there are four or more carbons in the acid chain and two or more carbons in the



alcohol chain, are sterically and chain-length controlled. In the study of deuterium-labelled *n*-butyl hexanoates (32a) and similar aliphatic esters[67], it has been established that the transfer of the hydrogen atoms occurs by stepwise processes. The first hydrogen migrates specifically from the γ-position of the acid chain to the oxygen function followed by migration of one or two hydrogen atoms chiefly derived from the second, third and fourth carbon atoms of the alcohol chain.



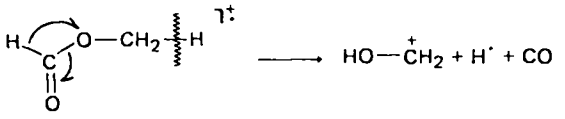
d. Loss of methanol from methyl esters. It was originally believed[59] that the formation of $[M - \text{MeOH}]^{\ddagger}$ ions in methyl esters involved a hydrogen rearrangement, probably from a γ-position. A review[68] on this subject has recently been published which summarizes the compelling evidence that:

(i) loss of MeOH from methyl esters requires protonation of the alkoxy oxygen;
(ii) the transfer of a hydrogen from the protonated carbonyl to the alkoxy oxygen does not occur in the mass spectra of esters (1,3-hydrogen transfer is a symmetry-forbidden process); and
(iii) hydrogen is abstracted almost exclusively to the carbonyl oxygen.

A mechanism has been proposed to account for the loss of alkanols from molecular ions of esters which requires the presence of a second functional group in the molecule acting as an intramolecular catalyst to promote the transfer of a proton from the carbonyl oxygen to the alkoxy oxygen.

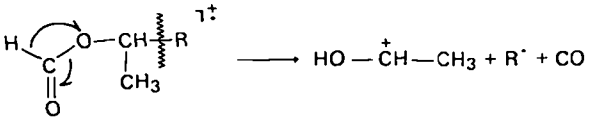
e. Specific rearrangements in short-chain esters. One of the characteristic ions in the mass spectra of simple formic acid esters appears at *m/e* 31 whose genesis is the result of an interesting rearrangement[48]. Methyl, ethyl and *n*-propyl formates all

give this rearrangement ion at *m/e* 31. By using methyl formate-d_1 (DCO_2CH_3), it has been established[69] that the formation of the ion at *m/e* 31(**ah**) from the ester (**33**) incorporates almost exclusively all the formyl hydrogen. The following fragmentation mode has been suggested:



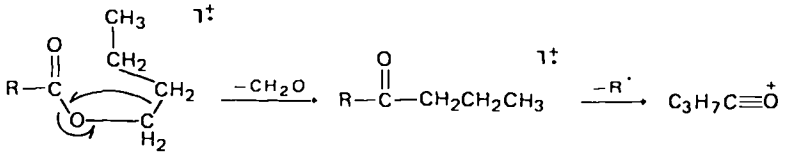
(**33**) (**ah**) *m/e* 31

The same mechanism of fragmentation can be applied to ethyl[70-72] and *n*-propyl formates giving rise to ion **ah** at *m/e* 31 together with $C_3^{\cdot}$ and $CH_3CH_2^{\cdot}$ radicals, respectively[69]. For isopropyl[70] and *s*-butyl formates (**34**) the characteristic ion (**ai**) is observed[48] at *m/e* 45 instead, and its formation follows the same mode of rearrangement.



(**34**) (**ai**) *m/e* 45

Other interesting rearrangement ions of the type $[M - CH_2O]^{\cdot+}$ have been observed[73,74] in *n*-butyl acetate and propionate (**35**). The genesis of these rearrangement ions is due to the migration of an alkyl radical to the carbonyl function, and at the same time cleavage of the C—O bond, giving rise to ions (**aj**) of similar structures to aliphatic ketones.

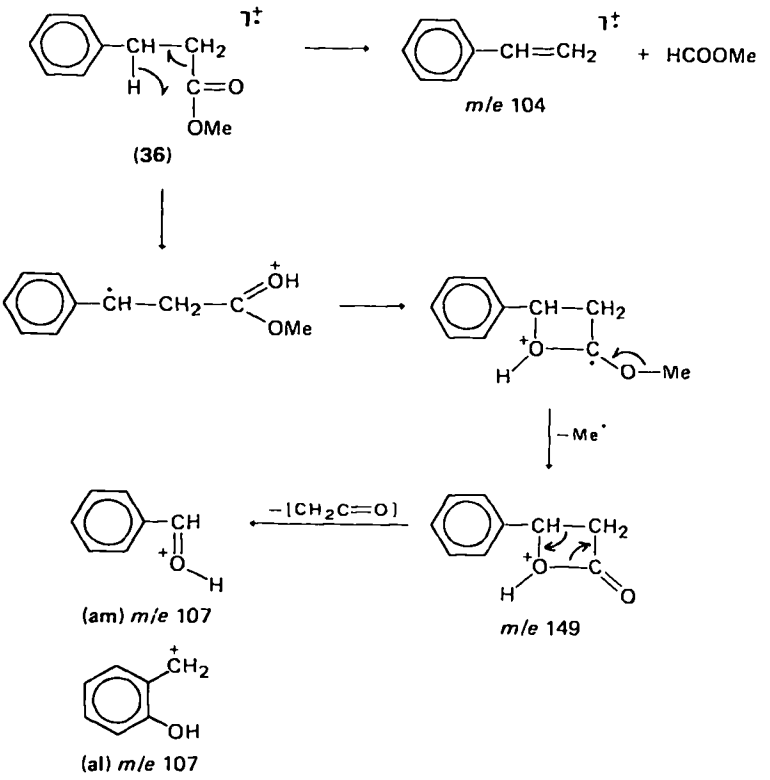


(**35**) R = CH_3 (**aj**) *m/e* 86 (**ak**) *m/e* 71
= CH_2CH_3 *m/e* 100

The above proposal has been substantiated[74] by studies of deuterium-labelled compounds.

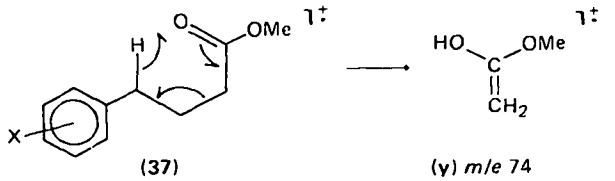
f. Alkyl phenylalkanoates. Of the esters of this class so far studied, alkyl 3-phenylpropionates have attracted much attention. By analogy to its parent acid, one of the major fragmentation modes registered[9] in the mass spectrum of methyl 3-phenylpropionate (**36**) is the expulsion of a molecule of methyl formate directly from its molecular ion.

Other rearrangement processes have been observed[75] for a series of 3-phenylpropionates. Formation of an ion at *m/e* 107 was originally believed[76,77] to involve the migration of the oxygen atom to the aromatic ring giving rise to an *o*-hydroxybenzyl ion structure (**al**). With ^{13}C labelling at the benzylic position, it has recently been shown[78] that this ion has in fact the structure of protonated benzaldehyde as depicted by ion structure **am**, whose mode of formation is suggested as shown below.



Elimination of a molecule of MeOH from the molecular ion of methyl 6-phenylhexanoate leads to the formation of prominent ions at $[M-32]^{+\cdot}$ and $[M-76]^{+\cdot}$; the structure of the latter ion is represented by f as in the case of hexanoic acid (**6**).

In the McLafferty rearrangement of methyl 4-phenylbutanoates (**37**), it has been found[79] that electron-withdrawing substituents on the phenyl ring have little, if any, effect on the rate of generation of ion y.



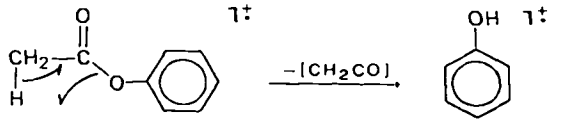
B. Aromatic Esters

Esters in which either the acid end or the alcohol end is occupied by an aromatic nucleus are considered to be aromatic. These include aryl esters, e.g. phenyl acetates, and esters of aromatic acids, e.g. methyl benzoates.

1. Aryl esters

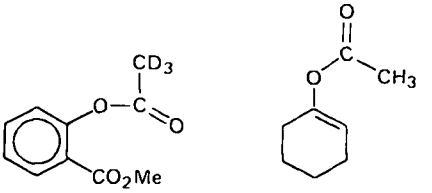
One of the common features in the mass spectra of phenyl acetates (**38**) is the observation of the $[M-CH_2CO]^{+\cdot}$ ions an at *m/e* 94 as opposed to the CH_3CO^+

ion formed by direct cleavage[80] of the C—O bond. Elimination of a ketene molecule from the molecular ions of aryl acetates occurs readily[81]. Detailed studies



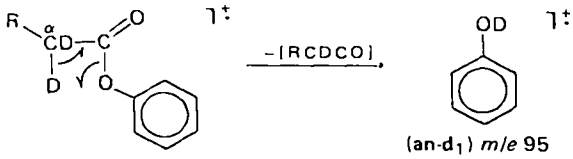
(38) (an) *m/e* 94

on the spectra of a series of deuterium-labelled phenyl acetates including methyl (O-d_3-acetyl)-salicylate (**39**) indicate[82] that the initial elimination occurs through a 4-membered transition state. This is in complete accord with the mechanism of ketene elimination from enol acetates[83], e.g. cyclohexenol acetate (**40**).



(39) (40)

The mass spectra of straight-chain esters such as phenyl butanoate and phenyl valerate (**41**) also reveal the formation of the rearrangement ion **an**. Extensive use of deuterium labelling has established[84] that approximately 90% of the hydrogen transfer is derived from the 2-position and the remaining 10% from hydrogen abstraction from other positions in the alkyl chain. Furthermore, the mechanism of the hydrogen transfer again follows a 4-membered transition as in the case of ketene elimination from phenyl acetate.[81].

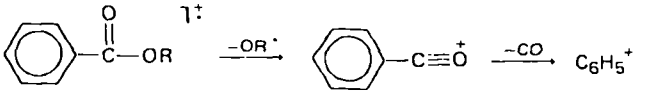


(41) (an-d_1) *m/e* 95

The mass spectra of a group of *m*- and *p*-substituted phenyl acetates and other esters have been studied widely and extensively in relation to the substituent effects[80,85,86]. It was concluded[86] that the fragmentation is affected by acyl substituents as well as aryl substituents. Esters that possess acyl groups of low ionization potential show greater changes in fragmentation because of aryl substituents, than those with acyl groups of high ionization potential.

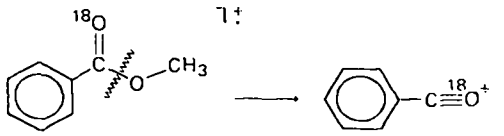
2. *Esters of aromatic acids*

a. Simple fragmentations. The most important fragmentation of simple alkyl benzoates[14] (**42**) is the production of the acylium ion (**ao**), which in turn loses CO to give the phenyl ion[87]. The mass spectra of several homologous series of aromatic esters have been studied and their fragmentation modes correlated with their molecular structures[88].



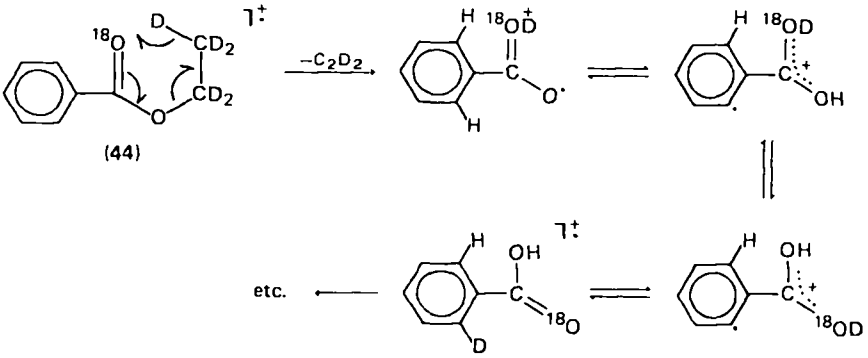
(42) (ao) *m/e* 105 *m/e* 77

Upon electron impact the carbonyl oxygen atom of methyl benzoate originally labelled with ^{18}O (**43**) was found[89] to remain exclusively in the benzoyl ion (ao-^{18}O) at *m/e* 107 providing that the carbonyl oxygen and the ether oxygen maintained their original identity during the fragmentation process.



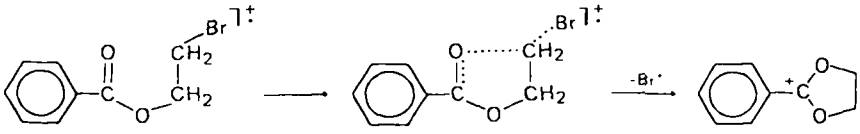
(43) (ao-^{18}O) *m/e* 107

b. Ethyl benzoates. In contrast to the exclusive retention of ^{18}O in the benzoyl ion generated from methyl benzoate, the mass spectrum of ethyl benzoate at 70 eV contains peaks both at *m/e* 107 and *m/e* 105 in the ratio of approximately 5:1. A prominent ion at *m/e* 124 for benzoic acid-^{18}O is also observed[89]. Further studies on extensively-labelled ethyl benzoates including a double-labelled compound **44** have established[90,91] that the oxygen atoms become equivalent after the elimination of an ethylene molecule as result of rearrangement. The transferred deuterium can only migrate further to the other oxygen atom through exchange reactions involving the *ortho* hydrogens of the ring after at least two complete rotations of the side-chain.



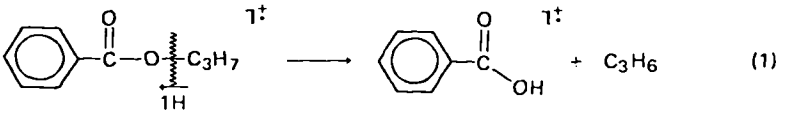
(44)

It is interesting to note that the expulsion of a bromine atom from the molecular ion of β-bromoethyl benzoate (**45**) affords an ion **ap** where the two oxygen atoms become equivalent in further decomposition. In fact, it has been established[92] that the $[M - Br^{\bullet}]^+$ ion (**ap**) has the same structure as the primary fragment ions resulting from the ethylene ketals of benzophenone or acetophenone.



(45) (ap) *m/e* 149

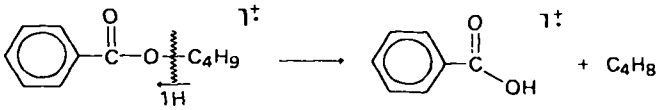
c. Hydrogen migration from the alcohol chain. For esters with three or more carbon atoms in the alcohol chain, transfer of hydrogens to the acid moiety in the same manner as aliphatic esters is observed. In *n*-propyl benzoate (**46**) the reactions



(46)

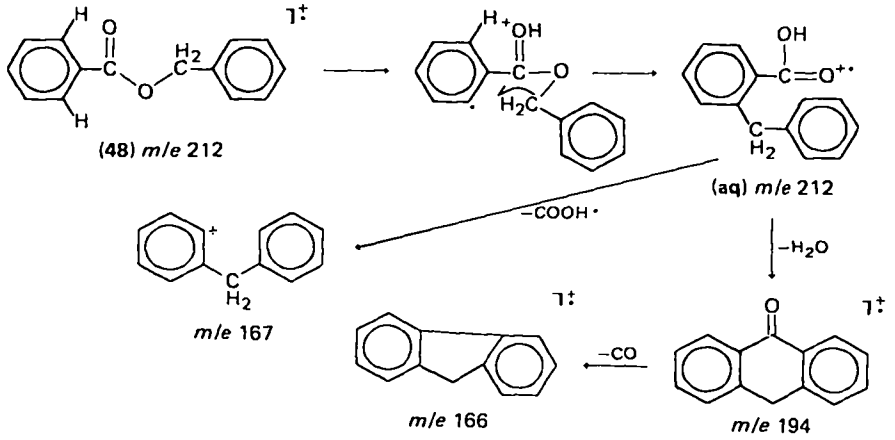
(1) and (2) are operative. It has been found[93] that in reaction (1), approximately 86% of the hydrogen is migrated from $C_{(\beta)}$ of the *n*-propyl chain. The specificity of the transfer from $C_{(\beta)}$ increases as the internal energy of the fragment ion decreases. In reaction (2), the migrations of the two hydrogens are derived almost exclusively one from each of $C_{(\beta)}$ and $C_{(\gamma)}$. It is noteworthy to mention that the $C_6H_5CO_2H^{+\cdot}$ ion generated from reaction (1) further fragments to give $C_6H_5CO^+$ and $OH^\cdot$ ions in a similar manner to the molecular ion of benzoic acid[15-17] but the interchange of hydroxy and *ortho* hydrogens occurs to a much lesser extent[93].

For *n*-butyl benzoate (**47**), the transfer of hydrogen is derived from $C_{(\beta)}$ to the extent of 78% and no other positions are involved in the hydrogen migration as evidenced by deuterium-labelling studies[74]. It appears, therefore, that a considerable 'isotope effect' discriminating against the transfer of deuterium is operative in this reaction.



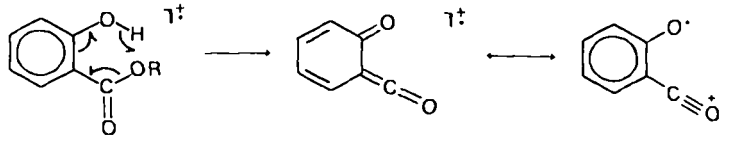
(47)

d. Benzyl benzoate. The molecular ion of benzyl benzoate fragments to yield prominent ions of $[M - H_2O]^{+\cdot}$ and $[M - CO_2H^\cdot]^+$. Loss of water from the

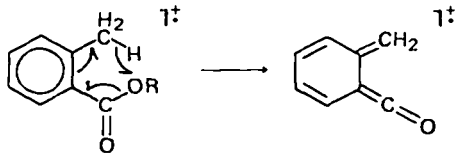


benzyl benzoate **48** has been shown[94] to occur via rearrangement processes. It has been established[94] that benzyl benzoate initially rearranges to ion **aq** which has the same structure as the molecular ion of α-phenyl-*o*-toluic acid (**aq**) prior to fragmentation.

e. ortho-*Substituted benzoates.* Similarly to *o*-substituted benzoic acids, elimination of a molecule of alcohol may occur if a substituent contains an α-hydrogen; e.g. in salicylates[20] (**49**) or *o*-methylbenzoates[14] (**50**).



(**49**)



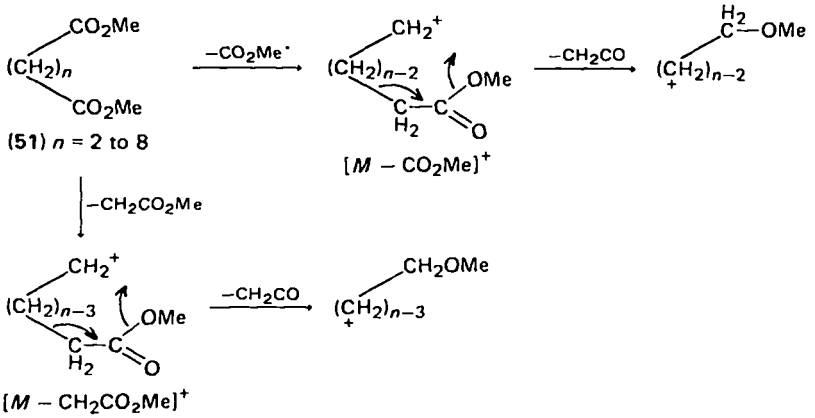
(**50**)

f. Methoxybenzoates. Examination of a series of alkyl esters of *meta*- and *para*-methoxybenzoic acid has revealed[95] that a new rearrangement is operative only in the *para*-substituted isomers. This involves the loss of HO• radicals from the molecular ions of *p*-methoxybenzoates. ^{18}O-Labelling studies have indicated[95] that the oxygen lost is solely derived from the carbonyl oxygen.

C. Dicarboxylic Esters

1. Aliphatic dimethyl esters

One of the common features of the mass spectra of simple dimethyl esters is the observation of migration of methoxy groups. In a study[96] of a series of aliphatic dimethyl esters (**51**, n = 1 to 8), two general migrations have been observed. Both reactions involve the loss of ketene from each of the fragment ions, $[M - CO_2Me^{\bullet}]^+$ and $[M - CH_2CO_2Me^{\bullet}]^+$, giving rise to the rearranged ions.

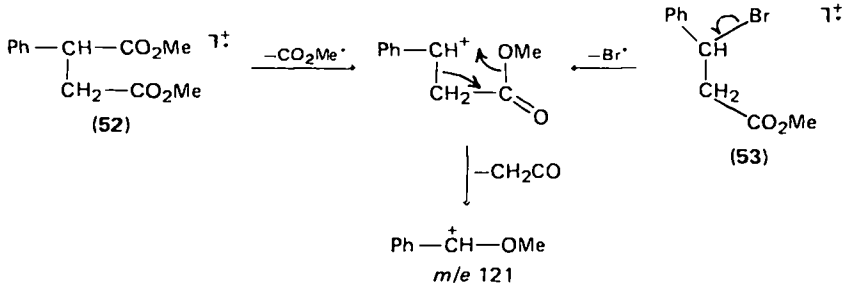


(**51**) n = 2 to 8

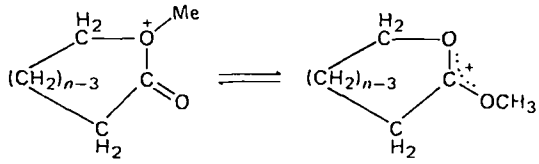
$[M - CO_2Me]^+$

$[M - CH_2CO_2Me]^+$

An example given to illustrate these general routes is dimethyl phenylsuccinate[38] (52) which fragments in an identical manner to methyl 3-bromo-3-phenyl propionate[97] (53) once the common intermediate is generated.



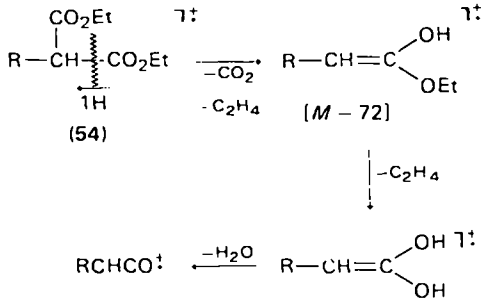
By plotting the appearance potential against n for loss of $^{\bullet}CH_2CO_2Me$ from **51**, it has been demonstrated[98] that the process is favoured for $n = 4$, 5 and 6 and that the stable ions $[M - {}^{\bullet}CH_2CO^2Me]^+$ probably possess cyclic structures (**ar**).



Polyfluoro dimethyl esters of **51** fragment in a distinctively different manner. Pronounced skeletal rearrangement occurs[99] and its mode of fragmentation can be summarized as $[M - CO_2 - C_2F_4 - C_2F_4]$.

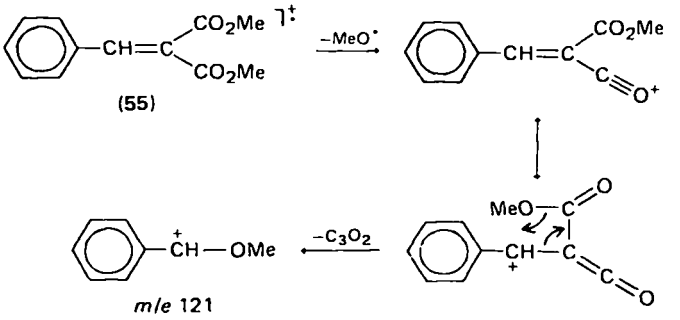
2. *Diethyl malonates*

With the alcohol chains each being increased by one more carbon as in the case of diethyl malonate (54), other fragmentation routes, in addition to those given above, have been suggested[100,101].



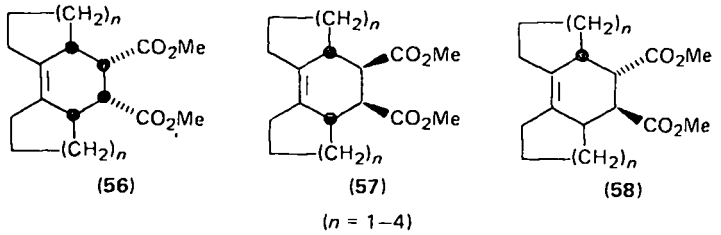
3. *Benzylidenemalonic esters*

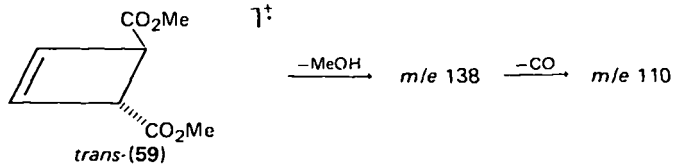
Dimethyl benzylidenemalonates[56] undergo fragmentation via a characteristic route of $[M - MeO^{\bullet} - C_3O_2]$. The loss of carbon suboxide as a neutral fragment is a relatively unusual phenomenon in carboxylic acid mass spectrometry[102].

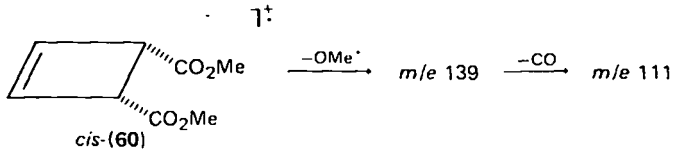


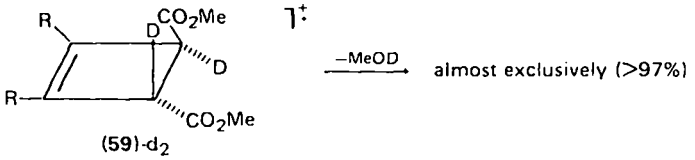
4. *Cycloalkene-1,2-dicarboxylic esters*

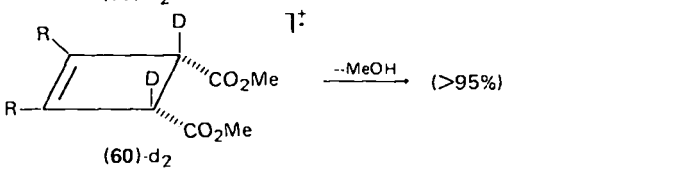
Stereospecific fragmentation processes in some rigid cyclic systems have been reported. Elegant work showing the effect of molecular geometry on the fragmentation of three series of stereoisomers **56**, **57** and **58**, $n = 1-4$, has been published[103].









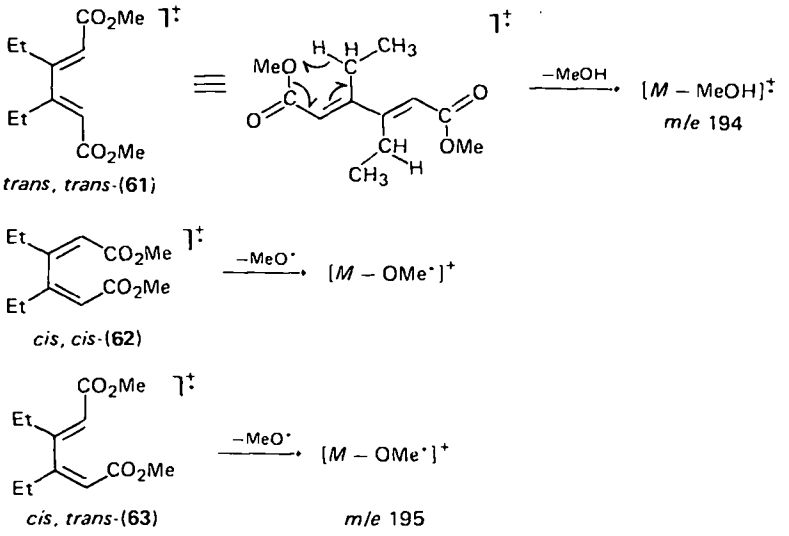


Endo-dimethyl esters of the **56** series all undergo elimination of methanol through a seven-centred transition state, whereas the stereoisomeric *exo* diesters of the **57** series expel a methoxy radical from each of the molecular ions. *Trans* diesters of the **58** series also eliminate a methanol molecule but through a five-centred transition state. It has been observed[103] that a further stereospecific hydrogen rearrangement accompanying retro Diels–Alder reaction occurs in the *endo* series.

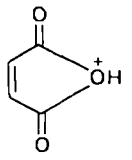
Stereospecific control of another pair of rigid stereoisomers has been recorded[104]. Expulsion of CH_3OH from the molecular ions of the dimethyl cyclobut-3-ene-1,2-dicarboxylates, **59** and **60**, occurs much more prominently in the case of the *trans* compound than its *cis* isomer. With the use of deuterium labelling, it has been shown[104] that the elimination takes place via different mechanisms in the stereoisomeric esters. Almost exclusive elimination of a mole of MeOD has been observed for the *trans* compound, but loss of MeOH only has been recorded for the *cis* isomer.

5. *Dimethyl muconates*

The mass spectra of a series of three different geometric isomers have been investigated[105] and interesting results in correlation with their stereoisomers have been reported. The molecular ion of the *trans, trans*-3,4-diethyl muconate (**61**) gives methanol upon electron impact whereas its *cis, cis*(**62**) and *cis, trans*(**63**) isomers eliminate methoxy radicals[105].

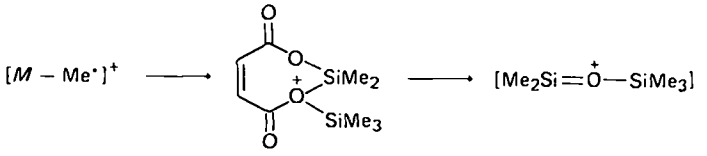


Another striking example of the influence of stereochemistry on the fragmentation mode of organic molecules is provided by the study of the mass spectra of maleates and fumarates. For a large number of dialkyl maleates which were studied[106] the base peak is observed at *m/e* 99 which corresponds to the protonated anhydride ion, as. The same ion is prominent, but is not the base peak, in the spectra of the isomeric fumarates[106]. In dimethyl maleate and fumarate, the intensities of the fragment ions at *m/e* 113 and *m/e* 85, generated by the routes of $[M - OCH_3{}^{\cdot} - CO]$, differ substantially for the two isomers[107].



(as) *m/e* 99

The use of bis-(trimethylsilyl) esters to differentiate the stereoisomers of maleic and fumaric acids has proved[108] to be successful. It has been shown[108] that the stereochemistry is maintained after ionization and as the *cis* maleate would be expected to form the intermediate ion at at *m/e* 245 more readily than the *trans* fumarate, *cis* maleate shows a more intense fragment ion at *m/e* 147.

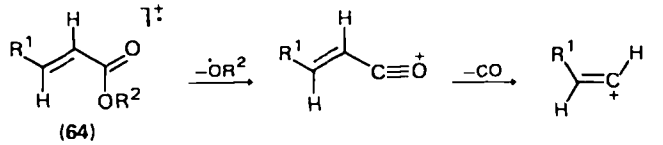


(at) *m/e* 245 *m/e* 147

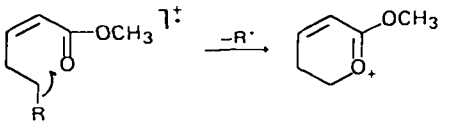
D. Other Esters

1. Unsaturated esters

Studies of α,β-unsaturated esters (64) have indicated that expulsion of an alkoxy group from the molecular ions followed by loss of CO are facile fragmentation processes[109,110]. Rearrangement involving alkoxy migration, although reported in



(64)

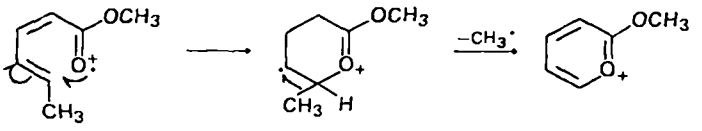


(65) (au) *m/e* 113

some esters[111], is not a major fragmentation mode[109]. No evidence of McLafferty rearrangement has been observed[109].

The base peaks in the spectra of a series of α,β-unsaturated esters (65) are obtained[112,113] by elimination of an alkyl radical with the formation of a 6-membered ring (au). Conjugated dienoic esters[114] such as methyl sorbate (66) tend to form a stable pyrylium ion (av) by the same mechanism as the formation of au.

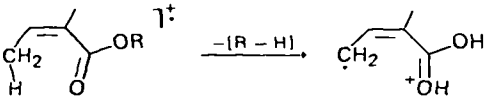
There is evidence that partial isomerization of molecular ions of β,γ-unsaturated esters[110] to α,β-unsaturated esters occurs, and their mass spectra show only small qualitative but strong quantitative differences[110]. Esters of γ,δ-unsaturated



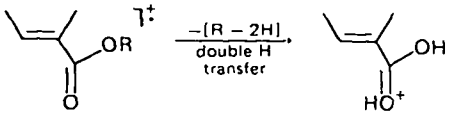
(66) (av) *m/e* 111

acids[76] fragment in a peculiar manner; elimination of the alcohol chain as a radical R• followed by the loss of a ketene molecule has been observed[76].

The mass spectra of the geometric isomers of α,β-unsaturated esters show significant differences in some cases which enable the double-bond geometry to be determined. Long-chain esters of 2-alkenoic acids[115] differ considerably in their mass spectra depending on the geometry of the double bond. 2-Methylbut-2-enoic esters[116] fragment in such a manner that the *Z* isomer (**67**) yields an abundant ion corresponding to the free acid (**aw**) while its *E* isomer (**68**) gives the protonated acid (**ax**).



(67) *Z* ester (aw) *m/e* 100

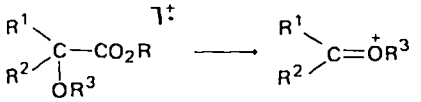


(68) *E* ester (ax) *m/e* 101

Esters of acetylenecarboxylic acids[106] and allenecarboxylic acids[117] have been studied. While loss of an alkoxy group from the molecular ions of acetylenecarboxylic esters[106] is the major fragmentation process, cleavage of the *O*-alkyl is observed as the principal feature in the case of allenecarboxylic esters[117].

2. *Hydroxy and methoxy esters*

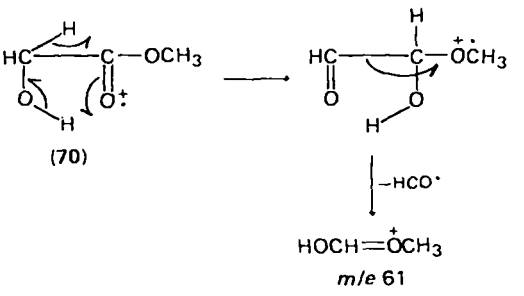
The most prominent fragment ions which appear in the mass spectra of esters of α-hydroxy or α-methoxy acids (**69**) are of the type $R^1R^2C{=}\dot{O}R^3$ (**ay**), which are derived[118] from their molecular ions. The methyl or ethyl esters of hydroxyacetic acid[118] (**70**) eliminate a formyl radical via rearrangement.

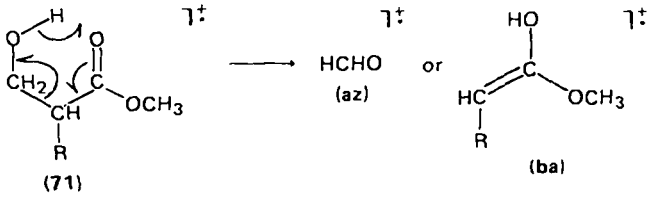


(69) (ay)

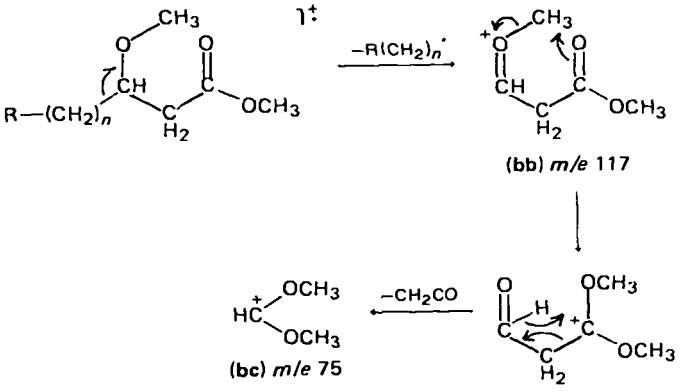
The characteristic feature in the fragmentation of α-substituted β-hydroxymethyl esters (**71**) is the β-cleavage with hydrogen transfer from the hydroxy function to the carbonyl group[119]; the degree of charge retention by **az** or **ba** is dependent upon the nature of the substituents.

One of the rearrangement ions which is characteristic in the mass spectra of the esters of β-methoxy acids is the observation of an intense peak at *m/e* 75. By using ^{18}O and deuterium-labelled analogues[120] it has been established that this ion at



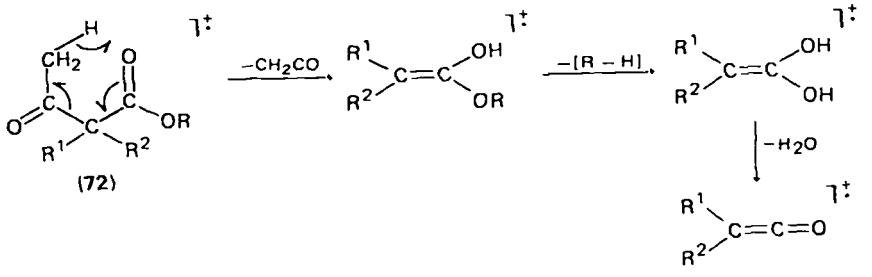


m/e 75 (bc) is derived from loss of ketene from the intermediate ion (bb) at *m/e* 117, which in turn is formed by the cleavage as shown. Other examples of β-methoxy esters which all give these characteristic ions at *m/e* 117 and *m/e* 75 have also been cited[120].

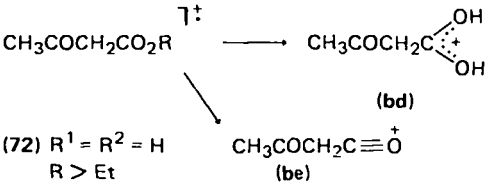


3. *Keto esters*

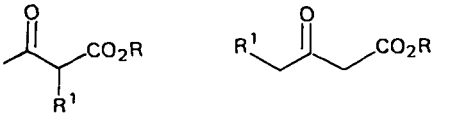
Alkyl acetoacetates (72) and their *C*-alkyl derivatives fragment, to a large extent, according to the following pathway[121].



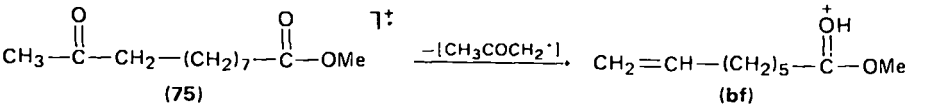
Loss of ketene from the molecular ion of 72 to form enolic fragment ions is a significant process for ethyl acetoacetate[122] (72, R = Et). If the R group becomes larger than ethyl, loss of the alkyl group R from the molecular ion with double hydrogen transfer to give an ion **bd** and elimination of the alkoxy radical to generate ion **be** are significant processes.



Comparison of the mass spectra of α-substituted (73) and γ-substituted β-keto esters (74) affords a useful method[123] of differentiating the α-and γ-substituted isomers. The most significant resultant ions are due to cleavage α to the keto carbonyl group and to McLafferty rearrangements[123,124]. One interesting observation[125] is the cleavage of a $CH_3CO—CH_2$ radical from the molecular ion of

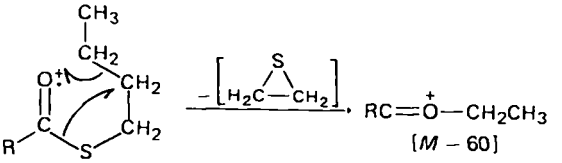


methyl 10-oxoundecanoate (75); the corresponding methyl undecanoate does not eliminate the $C_3H_7^{\bullet}$ radical. It has been suggested[125] that a hydrogen atom is initially transferred to the carboxycarbonyl prior to the fragmentation producing the ion **bf**.



4. Thio esters

The fragment ions $\left[CH_2=C\begin{matrix}OR\\OH\end{matrix}\right]^{+\cdot}$ and $RCO_2H_2^+$ observed in the spectra of aliphatic esters are only of minor importance in the sulphur-containing counterparts, whereas the ion $RCOO^+$, which is not observed in aliphatic esters, is encountered ($RCOS^+$) in thioesters[126]. Expulsion of a fragment of 60 mass units (SCH_2CH_2) is thought[126] to proceed via a cyclic intermediate.

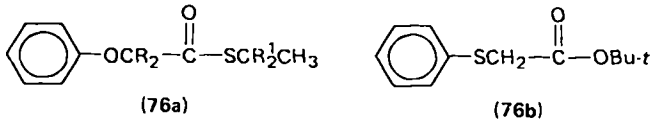


While thioglycollic esters fragment in the same manner as their parent acids[39], β-alkylthiopropionic ester generates rearrangement ions quite different from those

of its parent acid[40]. Methyl thionvalerate displays a large McLafferty rearrangement peak[56] at *m/e* 90.

Examination of the mass spectra of some alkyl phenoxythioacetates (76a) has revealed[127] an unusual rearrangement ion $[M - C_6H_5O - CO]^+$. Alkyl thiophenoxyacetates (76b) fragment via interesting rearrangement processes[128].

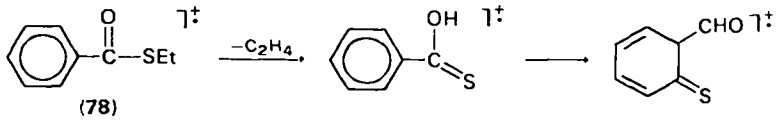
One of the major fragmentation pathways for aliphatic esters of aromatic dithiocarboxylic acids (77) is shown below[129,130]. Fragmentation involving rearrangement follow in the usual manner, as in the oxygen-containing homologue[129].



(76a) (76b)

(77) *m/e* 121 *m/e* 77

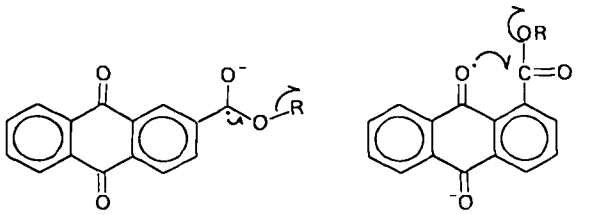
Migration of a sulphur atom to an *ortho* position in a *S*-ethyl thiobenzoate (78) has been reported[131].



(78)

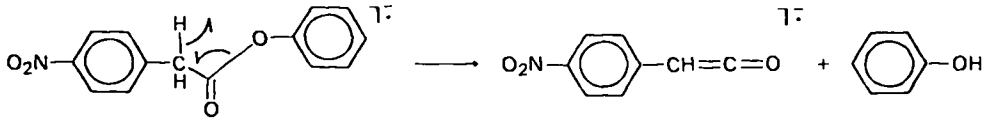
E. Negative-Ion and Chemical Ionization Mass Spectra of Esters

Negative-ion mass spectra of aliphatic esters have not been recorded. Those compounds that have been studied in greater detail include esters containing anthraquinone[132] and nitrophenyl[133-135] groups. The basic fragmentation of alkyl esters at the 1- and 2-positions of the anthraquinone system is $[M^{\cdot -} - R^{\cdot} - CO_2]$. Anthraquinone-1-carboxylates (79) also undergo fragmentation of $[M^{\cdot -} - RO^{\cdot}]$, experiencing the 'proximity effect'[132].



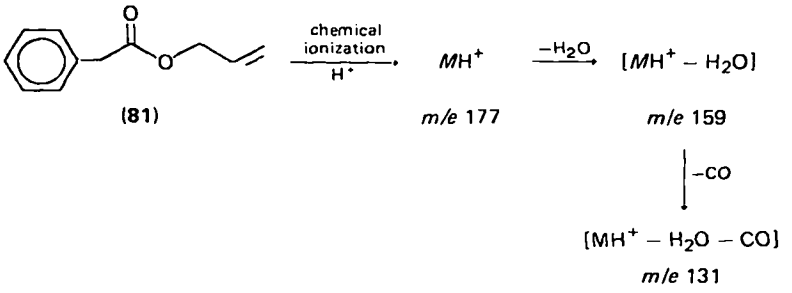
(79)

The main elimination from the phenyl (*p*-nitrophenyl)acetate (80) molecular anion[135] is loss of C_6H_5OH giving rise to anion **bg**. It is interesting to note[133] that the six isomers of nitrophenyl benzoates and phenyl nitrobenzoates are readily differentiated by their negative-ion mass spectra. Pronounced 'proximity effects' are observed[133] in the spectra of *ortho*-substituted compounds.



(80) (bg)

Chemical ionization of esters using methane at the reactant gas have been reported[136,137]. The mass spectra are well explained in terms of major reactions with CH_5^+, $C_2H_5^+$ and $C_3H_5^+$ producing $[M+H]^+$ ions which then fragment to give $RCO_2H_2^+$, RCO^+ and alkyl ions from the alcohol chain[136]. As an illustration, allyl phenylacetate (81) fragments in a typical manner[137] as shown.



(81) *m/e* 177 *m/e* 159 *m/e* 131

IV. AMIDES

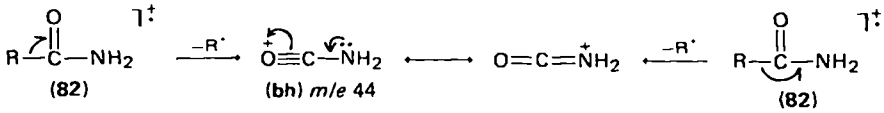
Unlike the esters, the majority of the amides so far studied contain an aromatic nucleus within the molecule. The studies of mass spectra of pure aliphatic amides are comparatively fewer than in the case of carboxylic acids or esters. Classification of amides in this section follows the general pattern as adopted in the previous two sections.

A. Aliphatic Amides

The mass spectra of a wide variety of aliphatic amides have been determined[138]. The results are consistent according to the fragmentations which are typical of alphatic carbonyl and amino groups.

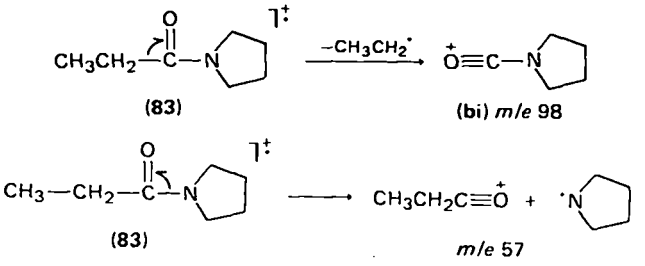
1. α-Cleavage

The most important fragmentation arises from α-cleavage in simple primary amides, such as formamide, acetamide, propionamide and isobutyramide[138] (82), giving rise to the common ion (**bh**) at *m/e* 44.



(82) (bh) *m/e* 44 (82)

Secondary amides such as 83 fragment in a similar manner[139]. Cleavage of the C—N bond leads to the formation of acylium ions which are also abundant in the mass spectra of aliphatic amides[139].

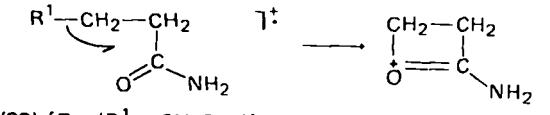


(83) (bi) *m/e* 98

(83) *m/e* 57

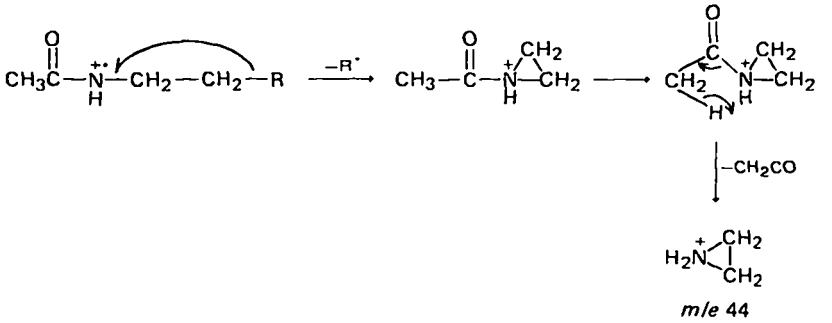
2. γ-Cleavage

γ-Cleavage in the mass spectra of amides has been observed[138] and is believed to operate via a four-membered ring system.



(82) [R = (R^1—CH_2CH_2)] (bj) *m/e* 92

In secondary and tertiary amides, if the carbon chains at the nitrogen end are sufficiently long, β- and γ-cleavages are also operative[140]. It is noteworthy that in



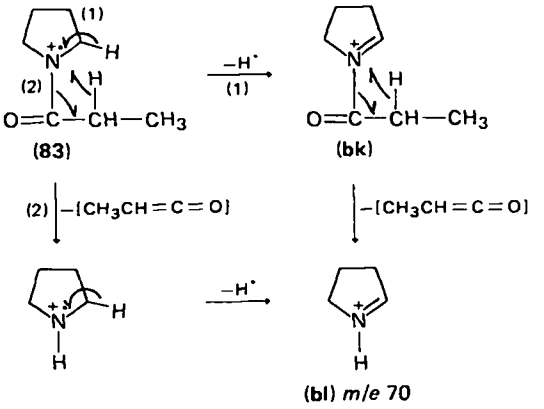
m/e 44

the spectra of tertiary amides, the predominant processes are those which also occur in secondary amide spectra.

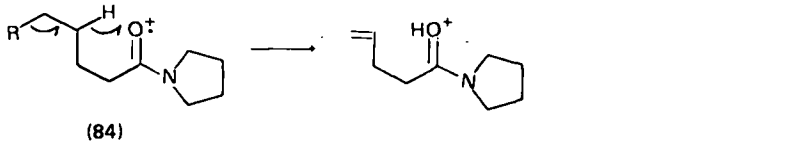
3. Fragmentation involving hydrogen migrations

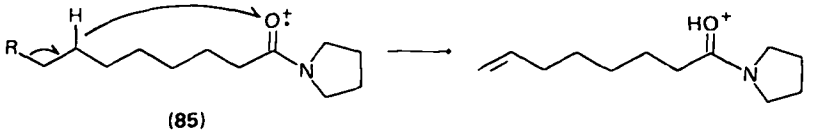
In analogy to acids and esters, if a three-carbon chain is available either at the acid end or at the nitrogen end, simple β-cleavage does not occur; β-fission would take place with hydrogen migration (McLafferty rearrangement)[138,139].

Elimination of an α-hydrogen atom from the molecular ion of 83 leads to the formation of species **bk** which in turn loses a ketene molecule to yield the ion **bl** at *m/e* 70. Alternatively, loss of a ketene molecule from 83 followed by the expulsion of a hydrogen radical[139] yields the same ion **bl**. Pronounced fragmentation at the β and γ bonds in the mass spectra of pyrrolidine amides, in contrast to carboxy and ester groups, makes them useful for the characterization of long-chain carboxylic

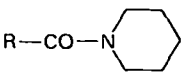


acids. Sometimes complications may arise because of non-specific hydrogen transfers as observed in the pyrrolidides 84 and 85[142].





Ring contraction has also been observed[143] in the mass spectra of *N*-acylpiperidides (86). For piperidides of high, saturated carboxylic acids, the ring-contraction process is only of minor importance[143]. While ring contraction is not observable in

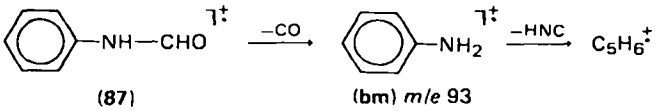


the mass spectra of 5-membered ring of pyrrolidides (e.g. 83), it is a significant process in the 7-membered homologues[144].

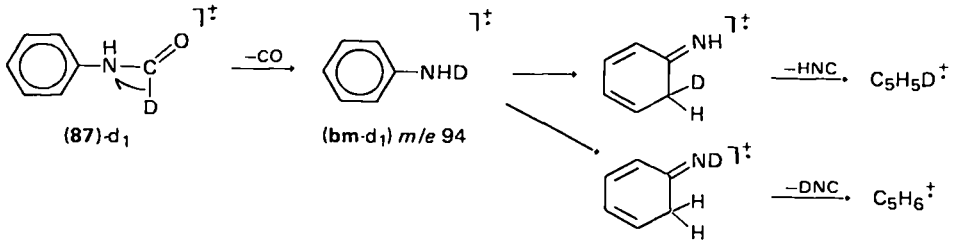
B. Aromatic Amides

1. Formanilides

Formanilide (87) fragments with the loss of CO from its molecular ion[145] to give an ion (bm), whose structure resembles aniline rather than cyclohexadienimine[146].

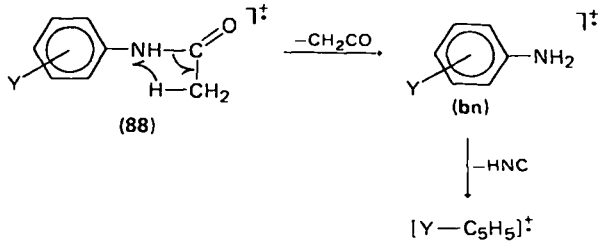


This statement has been substantiated by the study of deuterium-labelled analogues which confirms that the formyl hydrogen migrates to nitrogen prior to or during CO expulsion to form the ion **bm**. Furthermore, the presence of the *ortho*-methyl group in the molecular ion of (**87**) does not affect the above fragmentation mode.



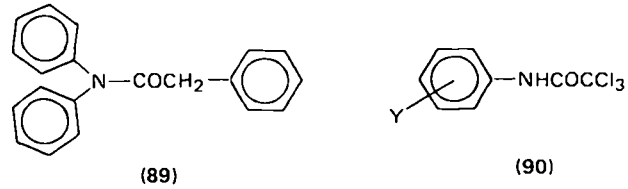
2. *Acetanilides*

From studies of steric effects on the relative intensities of the (**bn**) from substituted acetanilides (**88**), it has been suggested[80,146] that **bn** also possesses the aniline structure. The appearance potential-ionization potential values of the rearrangement reaction[147], the steric effects[148], the isotope effects[149] and the metastable peak abundance ratio[150] for the process of [**bn** – HNC] all strongly support the mechanism of ketene elimination occurring through a 4-membered



transition state. The [*M*-ketene] ions (**bn**) often appear as the base peaks in the mass spectra of aromatic anilides[151]. The other competitive fragmentation from the molecular ions of acetanilides **88** is the formation of the acetyl cation (CH_3CO^+) at the *m/e* 43 by a simple direct cleavage of the C–N bond[80].

Analogous behaviour has been observed[152] with other substituted acetanilides, e.g. *N,N*-diphenyl phenylacetamide (**89**), but the fragmentation of trichloroacetanilides (**90**) is different from acetanilide[153,154]. Elimination of $CCl_3^{\bullet}$ from the molecular ion of **90** is the primary and abundant fragmentation process.

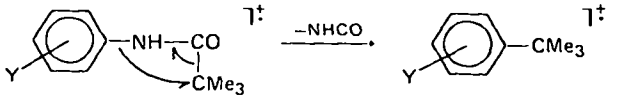


It may be of interest to note that while significant differences have been observed between the spectra of the three isomeric nitroacetanilides, the mass

spectra of the three isomeric methylacetanilides are very similar except for differences in the intensities of $[M - CH_3CO]^+$ and CH_3CO^+ ions[154].

3. Pivalanilides

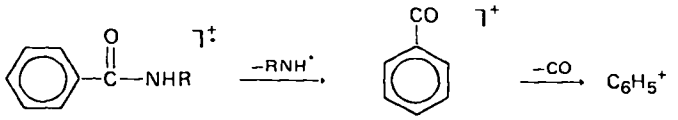
Substituted pivalanilides (**91**) give rise to fragments corresponding to anilines which are derived[155] from hydrogen transfer from the *t*-butyl group to the nitrogen similar to acetanilides. One interesting feature of these spectra[155] is the novel migration of an aryl group to the *t*-butyl carbon giving rise to the *t*-butylbenzene derivatives, **bo**.



(91) (bo) $[M - 43]$

4. Benzamides

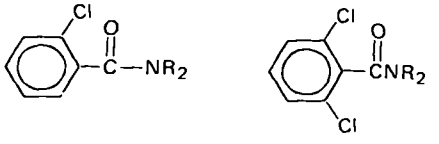
As expected, the major fragmentation from the molecular ion of unsubstituted benzamide (**92**) leads to the formation of a benzoyl ion, (**bp**) at *m/e* 105 which in turn fragments according to the following pathway[151,156,157]. *N*-(Substituted



(92) R = H
R = C_6H_4X (bp) *m/e* 105 *m/e* 77

phenyl) benzamides (92, R = C_6H_4X—) give spectra which are virtually identical to those of 92, R = H[156,157]. Pentafluorobenzamide[151] also behaves in a similar manner.

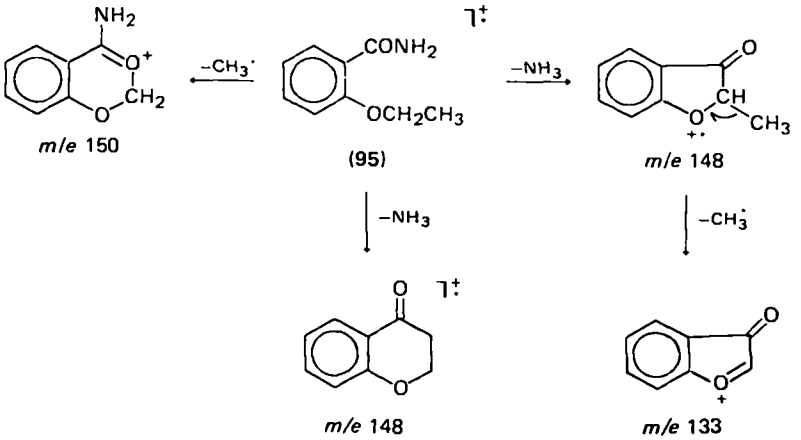
It should be of interest to note that although $[M - H^\bullet]^+$ ions are significant and abundant in the mass spectra of *N,N*-disubstituted benzamides[158–160], the corresponding $[M - H^\bullet]$ species does not occur in the mass spectrum of benzamide itself[160]. Furthermore, the $[M - H^\bullet]^+$ ion is more abundant in the case of *N,N*-disubstituted benzamides than in their corresponding *N*-monosubstituted analogues[160]. By the use of deuterium-labelled compounds, it has been shown[158,159] that the loss of a hydrogen atom is exclusively from the *ortho* hydrogens of the aromatic ring. The methyl hydrogens of *N,N*-dimethyl benzamides are shown[158,159] to be uninvolved. These results have been confirmed[160] by studies of the mass spectra of 2-chlorobenzamide (**93**) and 2,6-dichlorobenzamide (**94**), where in the latter case no $[M - H^\bullet]^+$ ion has been observed.



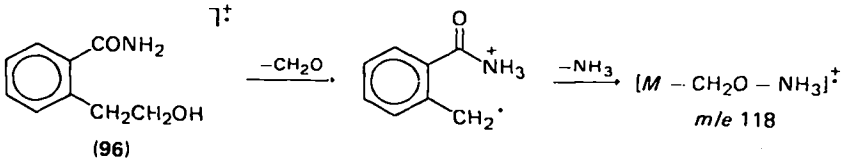
(93) (94)

Generally, it is concluded that isomers with substituents at the *meta* and *para* positions on the aromatic ring of benzamides give very similar mass spectra. In many cases, the spectra can hardly be differentiated[161]. However, *ortho*-substituted benzamides give distinctively different spectra from those of their *meta* or *para* isomers[23,161,162], and this is attributable to the so-called '*ortho* effects'.

In *o*-ethoxybenzamide (**95**), loss of a methyl radical and elimination of ammonia from the molecular ion are prominent fragmentation processes[161,163].



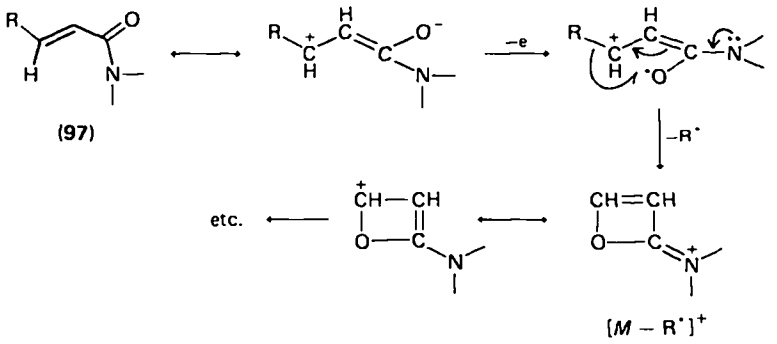
The mass spectrum of an isomer of **95**, *o*-(2-hydroxyethyl) benzamide (**96**), shows a fragmentation route, $[M - CH_2O - NH_3]$, as depicted below[164].



C. Other Amides

1. *Unsaturated amides*

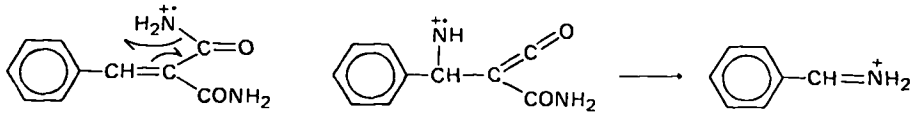
β-Substituted α,β-unsaturated amides (**97**) fragment preferentially via 4-membered cyclic transition states[113] giving rise mainly to ions of the type



$[M - R^{\bullet}]^{+}$. Cleavages of methyl groups from piperidides of formula $CH_3(CH{=}CH)_n CONC_5H_{10}$ with $n = 1-3$ have been recorded[165].

2. Diamides

It has been observed[166] that fragmentation of the molecular ion of benzylidenemalonamide (**98**) occurs with rearrangement yielding ions **bq**, which is analogous to the fragmentation mode of dimethyl benzylidenemalonate[102]. Another analogy that may be drawn between dicarboxylic esters and diamides is found in the double-bond geometric isomers such as maleic, fumaric, citraconic, mesaconic and itaconic amides. The amide–amide interaction[167] in *cis* isomers does take place but to a lesser extent than carboxy–carboxy interaction of the corresponding acids[35].

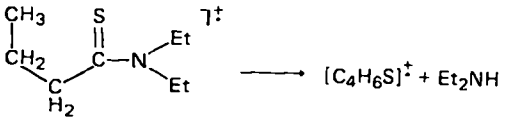


(98) (bq) *m/e* 106

3. Thio amides

Unlike benzoic acid where the *ortho* and the hydroxy hydrogen atoms scramble before the expulsion of the OH$^{\bullet}$ radical[16,17], scrambling between the *ortho* and the amino hydrogens does not occur prior to the loss of $NH_2{}^{\bullet}$ from the molecular ions of benzamide or thiobenzamide[168]. The fragmentation pathways between benzamide and thiobenzamide are virtually the same.

It has been observed[169] that in the mass spectrum of the thio amide **99** competitive reactions between the conventional rearrangement leading to the expulsion of ethylene and a second rearrangement route as illustrated below are both operative.

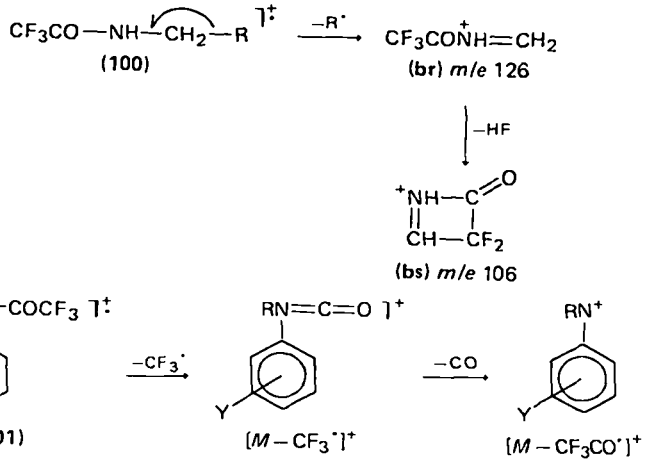


(99)

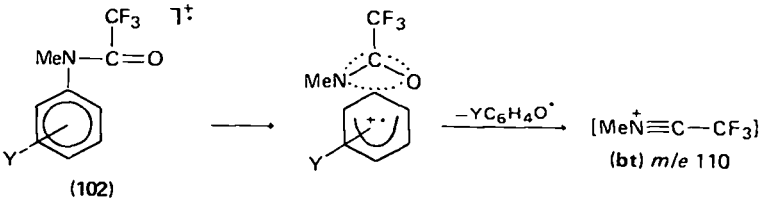
4. Trifluoroacetamides

N-Alkyl trifluoroacetamides (**100**) yield ions due to CF_3^+ and $[M - CF_3{}^{\bullet}]^{+}$ which are shown in their mass spectra. The intensities of molecular ions of *N*-methyl and *N*-ethyl trifluoroacetamides are high but rapidly diminish as the alkyl chain becomes longer[170]. The base peak in many straight-chain derivatives appears at *m/e* 126, depicted as **br**, which in turn expels one molecule of HF to give ion **bs**.

The molecular ions of all ring-monosubstituted derivatives of *N*-aryl trifluoroacetamides (**101**) are revealed in their mass spectra as base peaks. Sequential loss of $CF_3{}^{\bullet}$ and CO from the molecular ions are significant processes producing $[M - CF_3{}^{\bullet}]^{+}$ and $[M - CF_3CO^{\bullet}]^{+}$ as abundant ions. Unlike the aliphatic trifluoroacetamides, the appearance of $[M - COCF_3{}^{\bullet}]^{+}$ ions is unique in aromatic trifluoroacetamides[171].

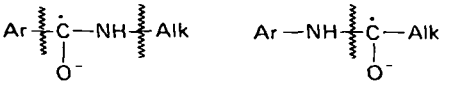


A novel rearrangement ion has been observed[172,173] in the mass spectrum of *N*-methyl trifluoroacetanilides (**102**, Y = H), which appears as a significant peak at *m/e* 110 and whose composition is shown to be [MeN ≡ C—CF_3] (**bt**). The genesis of the ion **bt** from the molecular ion, as supported by a strong metastable peak, indicates the elimination of a phenoxy radical. It has further been shown[174] that the cleavage of the phenoxy radical requires very little energy.



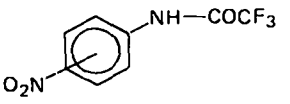
D. Negative-ion Mass Spectra of Amides

In aliphatic amides, negative-ion spectra are usually inferior to positive-ion spectra[43]; for example, only a weak $[M - H^{\bullet}]^-$ ion is observed in the spectrum of dimethylformamide. With aromatic amides, especially where there is a nitro substituent, fragmentations become more pronounced and negative ions more abundant. Cleavage of aryl amide molecules can be rationalized in the following two directions[175]:



The spectrum of *o*-nitrophenylacetamide[44] exhibits cleavage generating $[M - HO^{\bullet}]^-$, $[M - NO^{\bullet}]^-$ and $[(M - NO^{\bullet}) - CH_2CO]^-$ ions whereas these ions are absent in the spectra of the corresponding *meta* and *para* isomers[176]. Such discrepancies in fragmentation are attributable to '*ortho* effects'.

The positive-ion spectra of the three positional isomers of nitrophenyl trifluoroacetamide (**103**) are virtually identical, but the negative-ion spectra show distinc-

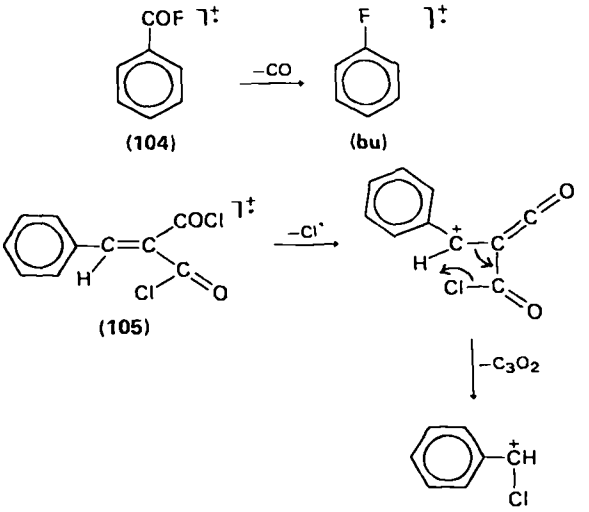


(103)

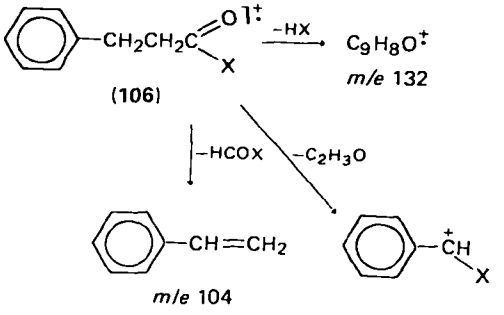
tively different features[177]. The *o* isomer fragments $HO^{\bullet}$, the *m* isomer cleaves according to the process $[M - HF - HO^{\bullet}]$ and the *p* isomer eliminates HF followed by a $H^{\bullet}$ atom[177].

V. ACYL HALIDES

Very few acyl halides have been studied in organic mass spectrometry. It has been recorded[178] that benzoyl fluoride (**104**) eliminates CO from its molecular ion giving rise to the ion of fluorobenzene (**bu**). Benzylidenemalonyl chloride (**105**) fragments with skeletal rearrangements in the same manner as the corresponding methyl esters[102].



One detailed study on the mass spectra of a series of 3-phenylpropionyl halides (**106**) has appeared in the literature[179]. The character of the halogen atom appears to have a marked influence on the fragmentation routes. Significant ions are revealed[179] in the spectra of these halides and they can be rationalized as follows:



VI. ANHYDRIDES AND IMIDES

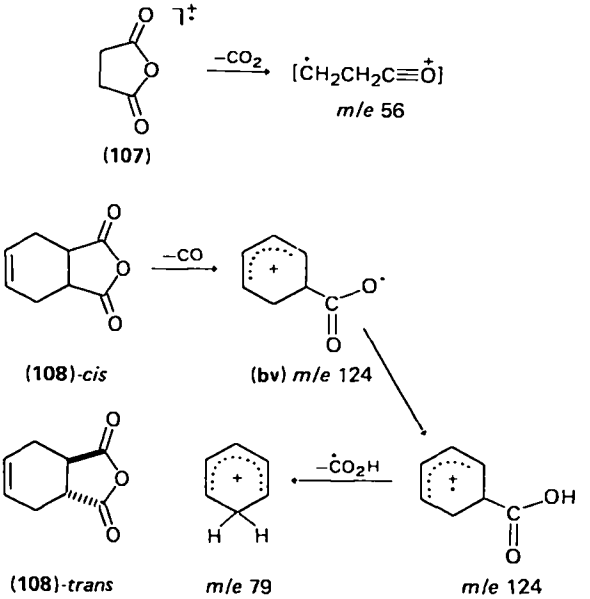
Both anhydrides and imides contain the partial structure —CO—X—CO—, where X = O in the case of anhydrides and X = N—R in the case of imides. In simple imides where X = NH or N—CH_3, fragmentations due to the functional groups of these two classes of compounds are similar; but when X = N-aryl or N-long-chain alkyl, there are added elements for mass spectral cleavage and the spectra usually become more complex than thoes of the corresponding anhydrides.

A. Anhydrides

1. Aliphatic acid anhydrides

The molecular ions of long-chain aliphatic acid anhydrides are completely absent from their mass spectra. The acylium ions are the base peaks[180], however.

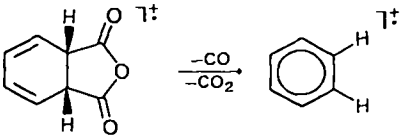
Cyclic anhydrides, e.g. succinic anhydride[181] (**107**) and tetrahydrophthalic anhydride[181,182] (**108**) do not afford molecular ions but give $[M - CO_2]^{\ddagger}$ and $[M - CO]^{\ddagger}$ ions, respectively. Elimination of CO from the molecular ion of **108** is



sterically controlled. The $[M - CO]^{\ddagger}$ ion (**bv**) is prominent in the mass spectrum of the *cis* isomer whereas this ion is almost absent in the corresponding *trans* isomer[182]. The striking difference in CO expulsion between the two isomers indicates that rearrangements do not occur prior to fragmentation. This is one of the classical examples that a high degree of stereospecificity is maintained during the fragmentation process.

1,2-Dihydrophthalic anhydride (**109**) fragments according to the following pathway[183]. Unlike the acyclic anhydrides and succinic anhydride discussed above, a strong molecular ion is observed[183] in the spectrum of **109**.

Other cyclic anhydrides that have been studied, including 3-acetoxy bicyclo-[2.2.2]oct-2-ene-5,6-dicarboxylic anhydride[184], all fragment in the same manner.



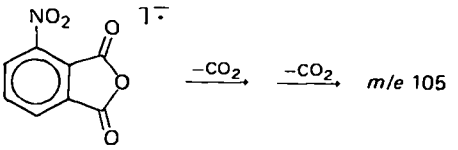
(109)

2. *Aromatic acid anhydrides*

Phthalic anhydride and its derivatives have been most widely studied. Phthalic anhydride, characteristic of aromatic anhydrides undergoes sequential loss of CO_2 and CO followed by the elimination of a molecule of acetylene[185-187]. Tetrachlorophthalic and tetrabromophthalic anhydrides also lose CO_2, CO and halogen atom (in that order) from their molecular ions[185].

3. *Negative-ion mass spectra of anhydrides*

In contrast to the simple and straightforward fragmentation of phthalic anhydrides in positive-ion spectra, negative-ion spectra of 3- and 4-nitrophthalic anhydrides contain a series of rearrangement anions. One feature of 3-nitrophthalic anhydride (**110**) is the successive loss from its molecular anion of two CO_2 molecules, one of which is derived from the CO of the anhydride moiety together with an oxygen of the nitro group[188].



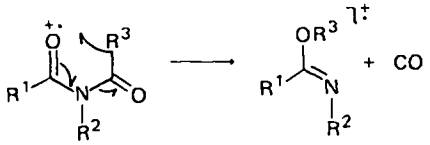
(110)

The conventional spectra of anhydrides produce only the molecular anions. Collisional activation[189] leads to the production of $[M - CO - CO_2]^{\cdot-}$ and $[M - C_2O_3]^{\cdot-}$ ions in phthalic anhydride. By the same technique, maleic anhydride shows the following ions: $[M - CO]^{\cdot-}$, CO_2 and C_2H^-. Ion cyclotron resonance study of negative ion–molecule reactions in anhydride systems have recently been presented[190].

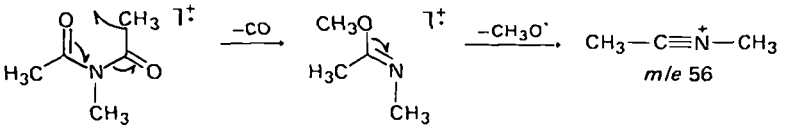
B. Imides

1. *Aliphatic acid imides*

Analogously to some β-diketones, acyclic imides undergo the following fragmentation as the initial cleavage of their molecular ions[191]:



As a general rule, should simple fragmentations be unfavourable processes in the mass spectra of imides, skeletal rearrangement ions are often observed. To illustrate the general fragmentation pathways, *N*-methyl acetylimide (**111**) is given[191] as an example.



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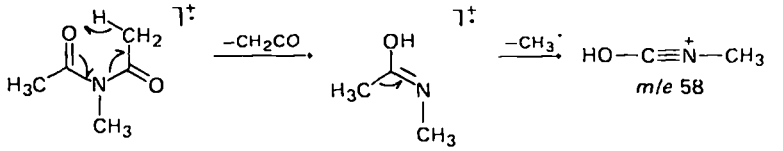
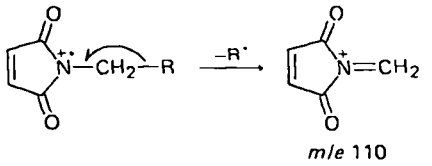
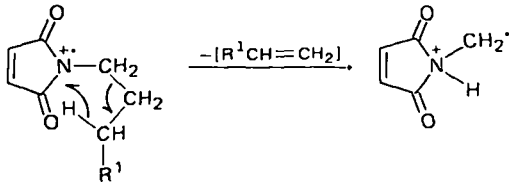
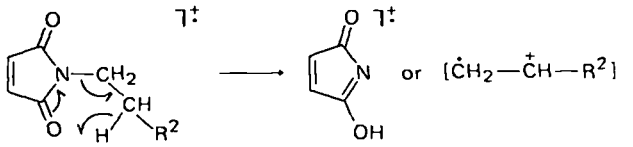


(111)

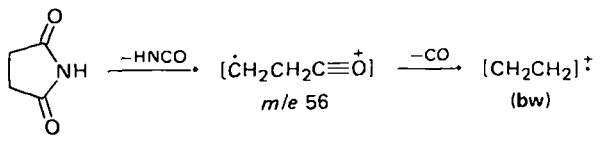
When the *N*-substituent chain is sufficiently long, cleavages of the chain, with or without hydrogen transfer, are also operative[192].







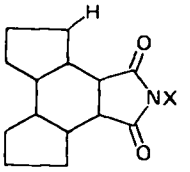
Similarly to succinic anhydride[181], where loss of CO_2 from the molecular ion is the initial and significant fragmentation, loss of HNCO from the molecular ion of succinimide (**112**) is the initial and prominent fragmentation process generating



(112)

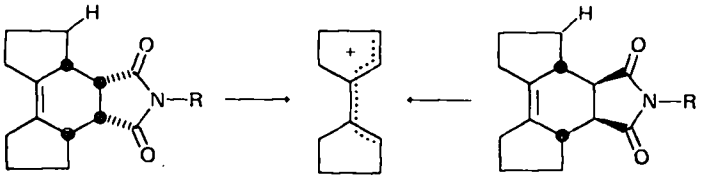
the acylium ion which in turn loses CO to form ion **bw**[193]. *C*-substitutions in succinimides do not alter the cleavage pathways[193,194] as given above, but *N*-substitutions[195] may lead to rearrangements with hydrogen migration similar to those in maleimides[195]. The spectra of saturated cyclic imides are almost identical to those of the corresponding diketones[196].

In polycyclic imides[197] where the molecules are rigid, stereospecific retro Diels–Alder fragmentation followed by hydrogen migration is found in the mass spectra of *endo–exo* isomers of **113**. The *endo* compound gives rise to an intense



(113)

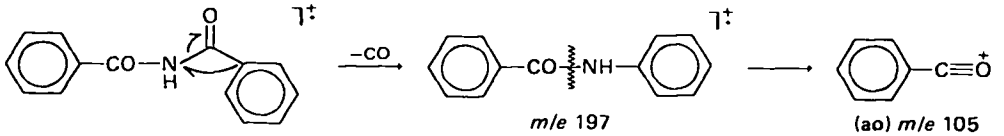
peak of ion **bx** (which constitutes the base peak of the spectrum) whereas the *exo* isomer gives rise only to a small peak[197].



(113)-*endo* (bx) (113)-*exo*

2. *Aromatic acid imides*

The fragmentation of the molecular ion of benzoyl imide (**114**) occurs in the following manner[191]:

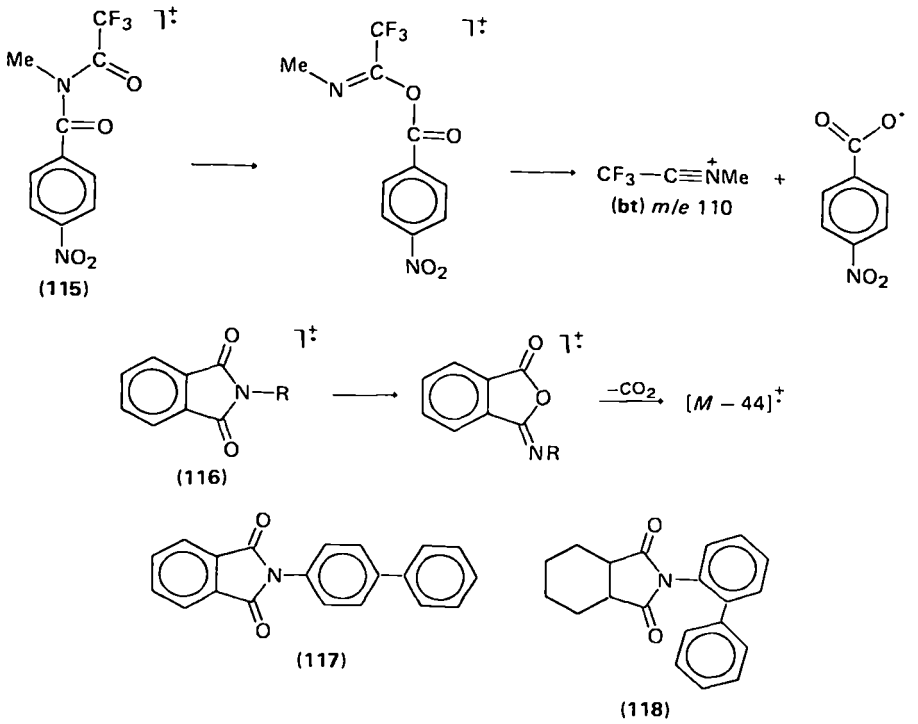


(114) *m/e* 197 (ao) *m/e* 105

Following a mechanism similar to the phenoxy radical migration in *N*-methyl-*N*-phenyltrifluoroacetamides[173,174], aroyl migration[198] in the imide (**115**) yields an ion at *m/e* 110 (**bt**).

Loss of CO_2 from cyclic imides may be regarded as occurring after aroyl migration[198]. In fact it has been observed[199–203] on several occasions, e.g. in the loss of CO_2 from phthalimides (**116**) upon electron impact. This rearrangement is considered[202,203] to arise by fragmentation of the isoimide, generated from the initial phthalimide.

It has been found[202] that when hydrogen transfer to oxygen is operative as in **117** loss of a hydroxy group, but not CO_2, is observed. The distinction between 4-phthalimidobiphenyl (**117**) and its isomer, 2-phthalimidobiphenyl (**118**), in their mass spectra has been identified[204,205]. Whilst loss of CO_2 is significant in **117**,



elimination of CO_2 from **118** is only of minor importance, But instead, **118** gives rise to prominent $[M - OH^{\bullet}]^+$, $[M - CHO^{\bullet}]^+$ and $[M - OH^{\bullet} - CO]^+$ ions[204].

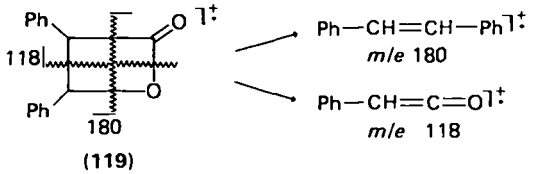
VII. LACTONES AND LACTAMS

The relationship between lactones and lactams should correspond to that between esters and amides. The mass spectra of several α-lactams have been studied but the mass spectrum of α-lactone has yet to be recorded. The main features of the spectra of other lactones and their corresponding lactams are fairly similar.

A. Lactones

1. β-Lactones

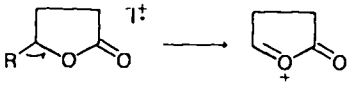
It has been observed[206,207] that β-lactones fragment in a simple manner. The main peaks appearing in the spectra are due to the splitting of two alternate bonds of the lactone rings. Substituted β-lactone (**119**) fragments according to the cleavage of bonds as shown[206].



(119)

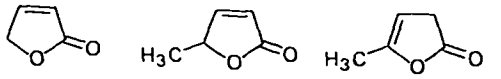
2. γ-Lactones

In general, the intensities of the molecular ions of γ-lactones in their mass spectra are usually low. For γ-lactones[208] of the general type, **120**, where R is a saturated alkyl group, the most important peaks appear at *m/e* 85 whose ion structure is represented by **by**[208,209]. For γ-butyrolactone[207] (**120**, R = H), the same fragmentation process occurs.



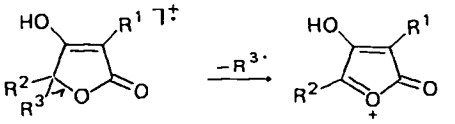
(120) (by) *m/e* 85

For unsaturated γ-lactones[207], e.g. crotonolactone (**121**), β-angelica (**122**) and α-angelica (**123**) lactones, the mass spectra are simple and show (1) much more intense molecular ions and (2) much larger intensities of fragment ions at *m/e* 55, 43 and 27.



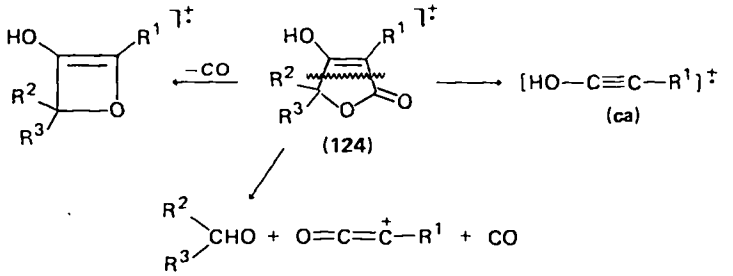
(121) (122) (123)

The mass spectra of the hydroxy-γ-lactone, tetronic acid (**124**) and a number of its derivatives have been reported[210,211]. Fragmentation of the molecular ions by



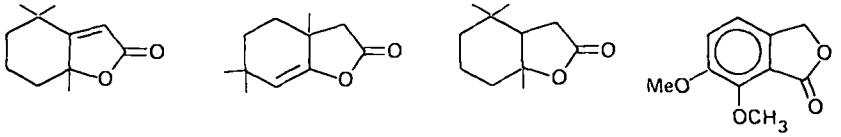
(124) (bz)

expulsion of the R^3 radical usually affords the base peaks (**bz**)[210]. Other fragmentations include the loss of CO from the molecular ion and fission of the ring system to produce ions of general type **ca**[211].



(124) (ca)

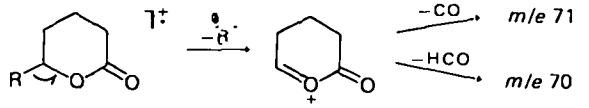
Several bicyclic γ-lactones (**125**–**128**) have been recorded[212,213] in the literature. The general fragmentation processes include the eliminations of methyl radical, CO and ketene[212]. For **128** the characteristic fission of H_2O involving the carbonyl group and the *peri*-OCH_3 group has been observed[213].



(125) (126) (127) (128)

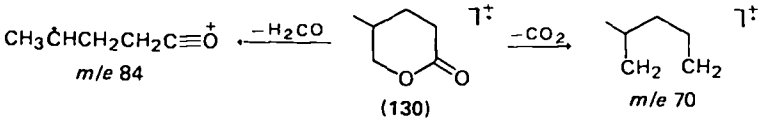
3. δ-Lactones

Similarly to γ-lactones, one of the most prominent fragmentations of the molecular ions of δ-lactones (**129**) is the expulsion of R• radicals, giving rise to ions of general structure **cb**[208,209]. The ion **cb** at *m/e* 99 and other ions at *m/e* 71, 70



(129) (cb) *m/e* 99

and 42 are typical, and the peaks are usually diagnostic for δ-lactones. It has been shown[214] that elimination of CO_2 is only important for a monosubstituted δ-lactone (**130**); another typical fragmentation mode common to all δ-lactones is the loss of the ring oxygen atom together with the adjacent carbon and its substituents in the form of a neutral carbonyl molecule such as formaldehyde, acetaldehyde or acetone[214].



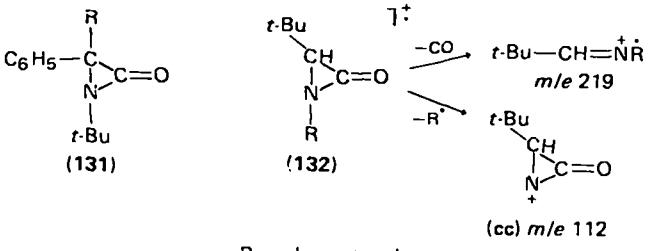
m/e 84 (130) *m/e* 70

B. Lactams

1. α-Lactams

In spite of the high strain in the molecules of α-lactams (aziridinones), the mass spectra of a series of this class of compounds have been studied.

A reasonably strong molecular ion peak has been observed[215] in the mass spectrum of the α-lactam (**131**, R = C_6H_5). The monophenyl analogue (**131**, R = H) gives a spectrum where the fragmentation ion can be rationalized according to the



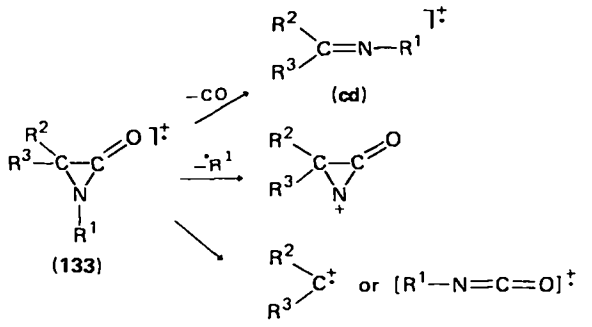
(131) (132) (cc)

R = adamantanyl

proposed structure. The initial and significant fragmentation of the molecular ion in the spectrum of **132** is elimination of CO, which is in sharp contrast with the thermal decomposition of α-lactams[216]. Cleavage of the N–C bond eliminates the adamantanyl radical generating the ion **cc** at *m/e* 112.

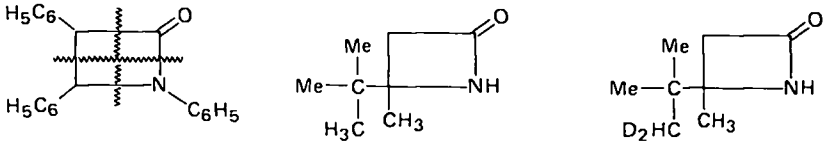
In those α-lactams of general formula **133** that have so far been studied, the majority of substituents at the ring carbon atom are *t*-alkyl or adamantanyl, or in one or two cases, phenyl[217-220]. No α-lactam with a secondary or primary alkyl group on nitrogen has been reported[217]. The major prominent fragmentation

process is elimination of CO forming the ion cd. Loss of R^1 as a radical or R^1-isocyanate are also significant processes[217-220].



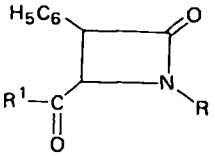
2. β-Lactams

The fragmentation of β-lactams occurs in a similar manner to that of β-lactones[206]. The mass spectra of β-lactams do not usually exhibit molecular ions but only fragment ions which are derived from cleavage as shown[221,222].



The mass spectra of **134** and its d_2-analogue have been compared[223]. Their base peaks appear at *m/e* 84 owing to loss of the *t*-butyl group. Since the base peak of the d_2-analogue remains at *m/e* 84, it indicates that the *t*-butyl group remains intact prior to fission. Further, in **134**-d_2 there is a new peak at $[M-17]^+$ due to elimination of $^{\bullet}CHD_2$.

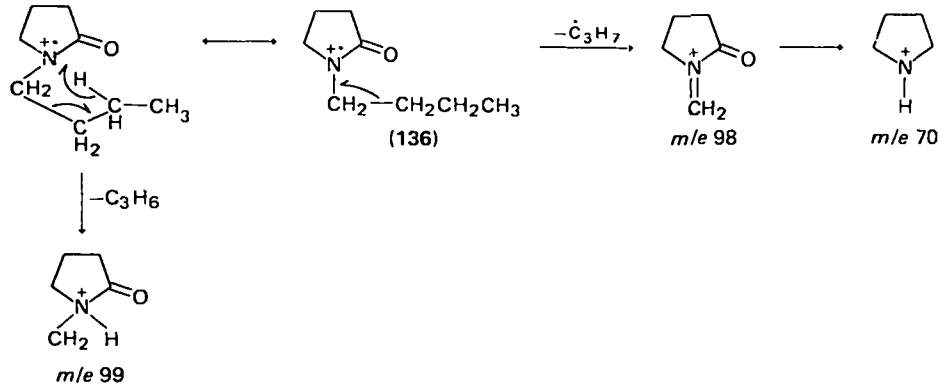
One unusual but interesting mode of fragmentation involving skeletal rearrangement is shown[224] in the mass spectra of β-lactams (**135**) by strong peaks at $[M-44]^{\ddagger}$ and $[M-45]^+$. Exact mass measurement has confirmed that $[M-44]^{\ddagger}$ is formed by elimination of CO_2. Isotope-labelling studies using ^{13}C at the ring carbonyl atom have revealed that the loss of CO_2 is derived from the lactam carbonyl together with the oxygen of the keto moiety in the chain through some form of skeletal rearrangement. The exact mechanism of formation has not yet been established[224].



3. γ-Lactams

N-methyl-γ-lactam shows essentially the same fragmentation behaviour as its parent compound[195]. Increase of chain length leads to degradation with or without

hydrogen migration. For example, *N*-*n*-butyl-γ-lactam (**136**) fragments according to the following scheme:



Other fragmentation routes of γ-lactams which involve ring-opening occur in a rather complicated manner[225]. One of the significant ions is revealed at *m/e* 30 whose structure is believed to be $CH_2{=}\overset{+}{N}H_2$. Ring-opening prior to fragmentation also occurs in large-ring lactams and the abundant ions in the spectra of caprolactam appear[226] at *m/e* 30 and *m/e* 44.

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER **5**

Complexes of acid anhydrides

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I. INTRODUCTION

This review concerns the use of acid anhydrides (referred to hereafter simply as 'anhydrides') as electron acceptors in weak interactions with other organic molecules acting as electron donors, in what are now generally described as electron donor–acceptor (EDA) complexes, or alternatively as charge-transfer complexes[1-5].

Theories as to the nature of the binding and the characteristic electronic absorption were suggested by various workers in the field including Briegleb[6], Weiss[7] and Brackman[8]. Some 25 years ago Mulliken[9] combined and developed a number of these earlier ideas in a valence-bond description. In the simplest terms, if a singlet electron donor (D) interacts with a singlet electron acceptor (A) then the ground state of the complex, $^1\psi_N(DA)$, may be represented as a linear combination of a no-bond structure, $^1\psi(D, A)$, in which A and D are held together by dispersion, dipole-induced dipole and similar forces, and a dative structure $^1\psi(D^+-A^-)$ in which one electron has been transferred from D to A. Thus:

$$^1\psi_N(DA) = a\,^1\psi(D,A) + b\,^1\psi(D^+ - A^-) \quad (1)$$

An excited singlet state of the complex, $^1\psi_E(DA)$, corresponds to the combination:

$$^1\psi_E(DA) = a^*\,^1\psi(D^+ - A^-) + b^*\,^1\psi(D, A) \quad (2)$$

the coefficient b^* being negative. The optical absorption characteristic of these complexes is identified with the transition $^1\psi_E(DA) \leftarrow {}^1\psi_N(DA)$. It is important to emphasize that in many organic EDA complexes, including those of anhydrides, the 'no-bond' structure is the major contributor to the ground state, that is $a \gg b$ in equation (1). Obviously in such cases there is little transfer of charge in the ground state, hence the criticism from some quarters of the term 'charge-transfer' as a description of these complexes.

By contrast with many other types of organic electron acceptors, anhydrides have been relatively slow in assuming a significant position in the field of EDA interactions. It is of interest to note that Pfeiffer[10], in his compilation of molecular complexes, listed very few complexes of anhydrides. Nearly all those mentioned by Pfeiffer are, in fact, complexes of halophthalic anhydrides: e.g. mesitylene, durene, naphthalene, anthracene, phenanthrene, naphthols and their ethers, *N,N*-dimethylaniline, *N,N*-dimethyl-*p*-toluidine and carbazole with tetrachlorophthalic anhydride; naphthalene and 1-ethoxynaphthalene with tetrabromophthalic anhydride; and acenaphthene with dichlorophthalic anhydride.

One experimental problem in the use of acid anhydrides is that the donor often undergoes chemical reaction with the anhydride, particularly in cases where water is

TABLE 1. Some anhydrides used in molecular complex formation

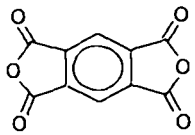
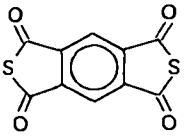
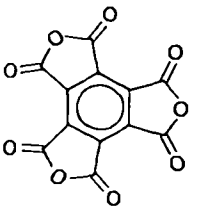
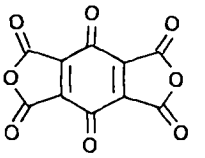
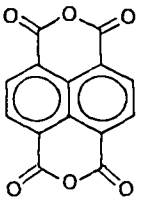
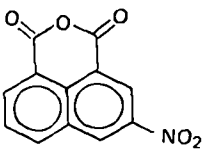
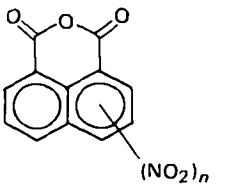
Name	Formula	Reference[a]
Maleic anhydride		13
Dichloromaleic anhydride		14
Dichloromaleic thioanhydride		15
Phthalic anhydride		
3,5-Dinitrophthalic anhydride		16
Tetrachlorophthalic anhydride		17
Tetrabromophthalic anhydride		18
Phthalic thioanhydride		19
Pyromellitic dianhydride		20, 21

TABLE 1. (continued)

Name	Formula	Reference[a]
Dithiopyromellitic dianhydride		15
Mellitic trianhydride		22–24
3,6-Di-oxo-1,4-cyclohexadiene-1,2,4,5-tetracarboxylic acid dianhydride		12
Naphthalene-1,4,5,8-tetracarboxylic acid dianhydride (and 2-bromo derivative)		25
3-Nitronaphthalene-1,8-dicarboxylic acid anhydride		26
Polynitro(2,5-; 3,6-; 4,5-; 2,4,5-)naphthalene-1,8-dicarboxylic acid anhydride		27

[a] References are intended to be illustrative, not exhaustive.

not scrupulously excluded. Thus the use of tetrafluorophthalic anhydride as an electron acceptor is, in practice, ruled out because of its extreme readiness to hydrolyse[11] although it is a strong acceptor and the fluorine nuclei would provide a useful probe in n.m.r. studies. Likewise, the high reactivity of *p*-benzoquinone tetracarboxylic anhydride severely limits the use of this interesting compound[12].

A second disadvantage of many acid anhydrides is their low solubility in non-polar aprotic solvents which are generally favoured by experimentalists in solution studies of EDA complexes.

A number of acid anhydrides which have been used in EDA complexation are listed in Table 1. This list is not intended to be exhaustive.

II. STABILITIES OF COMPLEXES IN SOLUTION

For EDA interactions in solution, it is generally assumed that the stoichiometry of the product is 1:1. In the majority of experiments the condition $[D]_0 \gg [A]_0$ has been used (the subscript zeros indicating the total, free and complexed, concentration of the particular species). This relative concentration condition is often dictated by the low solubility of the acceptor. Anhydrides are no exception; their solubilities in non-polar solvents are particularly low, which accounts for frequent employment of polar aprotic solvents such as acetic anhydride and ethyl acetate. There is also a good theoretical reason for using a large excess of one reagent, as has been pointed out by Person[28], and more recently by Deranleau[29]. These workers have shown that only by taking a range of solutions sufficient to achieve a wide change in the ratio of complexed to total concentration of one species [described by Deranleau as the 'saturation fraction' (s)] can sufficient information be obtained to evaluate satisfactorily the equilibrium quotient for the 1:1 complex, or to hope to detect the formation of complexes with other stoichiometries. In order to get a wide s range, the condition that one component is to be in large excess over the other is usually required.

The most common method of evaluating the equilibrium quotient, Q, under this condition is the method of Benesi and Hildebrand[30]. If a molar scale is used, Q may be defined as:

$$Q_c = [DA]/[D][A] \tag{3}$$

It is usually assumed that the quotient of activity coefficients $\gamma_{DA}/\gamma_D\gamma_A$ is sufficiently close to unity for the equilibrium quotient, Q_c, to be equated to the thermodynamic equilibrium constant K_c. Some workers prefer to use the mole-fraction scale. In Table 2 below, literature values on this scale have been converted to the molar scale using the ideal dilute solution relationship:

$$K_c = \upsilon K_x \tag{4}$$

where υ is the molar volume of the solvent in litres and K_x is the association constant on the mole-fraction scale. For a series of solutions in which $[D]_0 \gg [A]_0$, a plot of $[A]_0/A$ vs $1/[D]_0$ should be linear (A = absorbance due to DA). From the intercept and gradient, K_c and the molar decadic absorption coefficient (extinction coefficient), ϵ, may be calculated. If complexes with other stoichiometries are formed along with DA, then the Benesi–Hildebrand plot should be non-linear[29]. In fact, for π-donor–π^*-acceptor interactions, although there is other evidence for multiple equilibria, the parameters are of such magnitudes that there is no observable deviation from linearity. From the same data, an alternative plot, namely, $A/[D]_0[A]_0$ vs $A/[A]_0$ can be used to evaluate K_c and ϵ[31,32]. This plot

was originally described by Scatchard[33] and is much more sensitive to the existence or otherwise of multiple equilibria.

As an alternative to using optical absorbance, the n.m.r. line position of the nucleus in the acceptor is now often used in experimental determinations of K[34]. If Δ is the difference in line position of a nucleus in the acceptor species in a solution containing a concentration $[D]_0$ of donor ($[D]_0 \gg [A]_0$) compared with a solution in which $[D]_0 = 0$, then the term Δ replaces $A/[A]_0$ in the functions plotted in the Benesi–Hildebrand and Scatchard equations. The parameter corresponding to ϵ is Δ_0, the chemical shift of the measured nucleus in the undissociated complex relative to the shift of the same nucleus in the free acceptor. Ganter, Newman and Roberts[35] observed changes in both ^1H and ^{13}C chemical shifts of maleic anhydride as the solvent composition was altered. They attributed these effects to specific interaction between solvent and solute molecules. No estimates of the degree of association were made.

A number of other methods for determining the association constants of EDA systems have recently been reviewed[36].

Measurements at a single temperature will not differentiate between isomeric 1:1 complexes should they exist. The value of K obtained from experimental data will represent the sum of the values of K for all such isomeric complexes[37]. In principle it might be possible to detect isomeric complexes with sufficiently different enthalpies of formation by a temperature dependence of the experimentally determined standard enthalphy of formation. To the reviewer's knowledge no such dependence has been observed for this type of complex. However, Wells[14] has suggested that the rapid decrease in apparent molar absorption coefficient with increasing temperature for the dichloromaleic anhydride complex of durene, and to a lesser extent for those of pentamethylbenzene and hexamethylbenzene, could be explained in terms of a changing proportion of isomeric complexes.

As indicated above, the solubility constraint has usually limited experimental studies to solutions in which $[D]_0 \gg [A]_0$. Most of the earlier studies were based on measurements of absorbance within the intermolecular charge-transfer band(s) of the complex(es) and for which the assumption was made that only 1:1 association was occurring. In some recent optical determinations of, for example, tetrachlorophthalic anhydride systems, Nagy, Nagy and Bruylants have purposely used Scatchard plots with wide saturation-fraction ranges[38]. They have reported no evidence of 2:1 complexing. N.m.r. measurements have been made for one or two similar systems and evaluated by the Scatchard method[39,40]. Again, no evidence has been obtained for 2:1 complexing. By contrast, the wavelength dependence of the apparent values of K for the dichloromaleic anhydride complexes of durene, pentamethylbenzene and hexamethylbenzene has led Wells[14] to suggest that complex formation of higher order is occurring alongside the normal 1:1 association in these systems. Further investigation of these systems should be made. The optical absorptions of solutions of maleic anhydride and of phthalic anhydride with the donors 2,6-dimethylnaphthalene and biphenyl in various solvents including dioxan, ethyl acetate and acetic anhydride have been analysed in terms of 1:1, 2:1 and 1:2 complexing[41]. However, the formation constants for the latter are very much larger than for the corresponding 1:1 association. Indeed, at some wavelengths negative values are obtained for the 1:1 association. It was suggested that this might be due to an overlap of absorptions of the complex and components. If such an artefact is present in the method of analysis, then the values obtained for the association constants are meaningless. Similar observations have been reported for anhydride complexes of biphenyl[42].

TABLE 2. Equilibrium constants for some EDA complexes, together with their wavelengths (λ_{max}) and absorption coefficients (ϵ_{max}) of maximum absorption in the intermolecular charge-transfer band

Acceptor	Donor	Solvent	T (°C)	K_c(l mol^{-1})	λ_{max}(nm)	ϵ_{max}(l mol^{-1} cm^{-1})	Reference
Maleic anhydride	Benzene	$CHCl_3$	25	0.051[a]			43
	Toluene	$CHCl_3$	25	0.048[a]			43
	Mesitylene	$CHCl_3$	25	0.088[a]			43
	Hexamethylbenzene	$CHCl_3$	25	0.10–0.18[a]			43
	Anthracene	$CHCl_3$	25	0.11–0.19[a]			43
	Anisole	$CHCl_3$	25	0.064[a]			43
	Styrene	$CHCl_3$	25	0.10[a]			43
	N,N-Dimethylaniline	$CHCl_3$	25	0.10[a]			43
	Acenaphthene	ClH_2ClCH_2Cl	20	0.7 ± 0.03			44
	Hexamethylbenzene	MCXA[b]	25	1.5 ± 0.2	340	2420 ± 200	45
	Thiophen	$CHCl_3$	~20	0.02 ± 0.01	270	10,300	46
	Furan	$CHCl_3$	~20	0.03 ± 0.00	292	3060	46
	N-Methylpyrrole	$CHCl_3$	~20	0.15 ± 0.01	345	1470	46
	Benzene	$CHCl_3$	~20	0.09 ± 0.02	276		46
	Mesitylene	CCl_4	r.t.[c]	0.33[a]	~300	1900	13
	Benzene	CCl_4	20	0.4[a]			47
	Mesitylene	CCl_4	20	1.2[a]			47
	Styrene	$CHCl_3$	25	0.27			48
	Styrene	MeCOMe	25	0.20			48
	Vinyl acetate	$CHCl_3$	25	0.064			48
Dichloromaleic anhydride	Benzene	$CHCl_3$	25	0.050–0.058[a]			43
	Anisole	$CHCl_3$	25	0.10–0.11[a]			43
	Durene	CCl_4	r.t.[c]	1.08	360		14
	Pentamethylbenzene	CCl_4	r.t.[c]	2.40	372		14
	Hexamethylbenzene	CCl_4	r.t.[c]	4.64	390		14
Phthalic anhydride	Triethylamine	EtOAc	20	0.3	298		49
	DABCO[d]	C_6H_6	20	0.9	299		49
	DABCO[d]	EtOAc	20	0.3	298		49
	Acenaphthene	CH_2ClCH_2Cl	20	0.1			44
4-Nitrophthalic anhydride	Triethylamine	C_6H_6	20	4			49
Tetrachlorophthalic anhydride	1-Bromonaphthalene	CCl_4	22	2.8	345	1060	50
	9-Bromophenanthrene	CCl_4	22	11	350	1000	50
	9-Bromoanthracene	CCl_4	22	10	425	1000	50
	3-Bromopyrene	CCl_4	22	16	415	880	50
	7-Bromobenz[*a*]anthracene	CCl_4	22	16	415	920	50
	Hexamethylbenzene	n-C_6H_{14}	r.t.[c]	34	383		17
	Hexamethylbenzene	C_6H_6	r.t.[c]	2.3	384	1950	17

	Hexamethylbenzene	CCl_4	r.t.[c]	14.0	391	1700	17
	Hexamethylbenzene	$(n\text{-}Bu)_2O$	r.t.[c]	13.0	381	1800	17
	Hexamethylbenzene	C_6H_5F	r.t.[c]	2.7	386	1750	17
	Hexamethylbenzene	$C_6H_5CF_3$	r.t.[c]	6.4	382	1500	17
	Hexamethylbenzene	cyclo-$C_5H_{10}CO$	r.t.[c]	2.4	373	1800	17
	Naphthalene	CCl_4	28	2.8	354		51
	Phenanthrene	CCl_4	28	7.29	368		51
	Anthracene	CCl_4	28	10.26	435		51
	Pyrene	CCl_4	28	10.00	425		51
	Biphenyl	CCl_4	28	2.90	343		51
	Stilbene	CCl_4	28	5.50	350		51
	Acenaphthene	CCl_4	20	5.6 ± 0.2	406	1050 ± 300	38
	Acenaphthene	CH_2ClCH_2Cl	20	2.1 ± 0.1	411	940 ± 100	38
	Acenaphthene	*n*-BuCl	20	3.2 ± 0.15	402	1000 ± 150	38
	Acenaphthene	C_6H_6	20	1.2 ± 0.04	408	1050 ± 20	38
	Acenaphthene	EtOAc	20	1.5 ± 0.05	400	930 ± 25	38
	Acenaphthene	THF[e]	20	0.5 ± 0.01	397	1400 ± 70	38
	DABCO[d]	EtOAc	20	8.5	436		49
	2-Methoxynaphthalene	CH_2ClCH_2Cl	20	1.7 ± 0.07	~385	1170	52
	Phenanthrene	CH_2ClCH_2Cl	20	3.0 ± 0.1			52
	Durene	CH_2ClCH_2Cl	20	1.2 ± 0.09			52
	Triethylamine	CH_3CN	20	3.3			53
	Triethylamine	EtOAc	20	5.3			53
	Triethylamine	THF[e]	20	2.2			53
	Triethylamine	*n*-BuCl	20	13.3			53
	Triethylamine	CH_2ClCH_2Cl	20	13.0			53
	Triethylamine	*n*-HexCl	20	10.0			53
	Triethylamine	CH_2Cl_2	20	15.0			53
Tetrabromophthalic anhydride	Acenaphthene	CH_2ClCH_2Cl	20	1.8 ± 0.05			44
3,6-Dichlorophthalic anhydride	Acenaphthene	CH_2ClCH_2Cl	20	0.8 ± 0.04			44
3,5-Dinitrophthalic anhydride	Acenaphthene	CH_2ClCH_2Cl	20	2.5 ± 0.1			44
4-Nitrophthalic anhydride	Acenaphthene	CH_2ClCH_2Cl	20	~0.6			44
Pyromellitic dianhydride	Benzene	CCl_4	26	0.293[c]	330	1030	54
	Toluene	CCl_4	26	0.483[c]	346	1670	54
	o-Xylene	CCl_4	26	0.99[c]	342	1710	54
	m-Xylene	CCl_4	26	0.730[c]	344	1750	54
	p-Xylene	CCl_4	26	0.792[c]	354	1210	54
	Ethylbenzene	CCl_4	26	0.545[c]	346	1670	54
	i-Propylbenzene	CCl_4	26	0.371[c]	344	1380	54
	t-Butylbenzene	CCl_4	26	0.384[c]	348	1260	54
	Anisole	CCl_4	26	0.744[c]	385	775	54

	Chlorobenzene	CCl_4	26	0.200[c]	340	1490	54
	Phenanthrene	$CHCl_3$	25	7.0	407	1410	55
	Naphthalene	$CHCl_3$	25	2.8	413	1033	55
	Triphenylene	$CHCl_3$	25	16.4	414	1470	55
	Fluoranthrene	$CHCl_3$	25	23.8	420		55
	Fluorene	$CHCl_3$	25	2.3		893	55
	Hexamethylbenzene	$CHCl_3$	25	2.2	437	1887	55
	Chrysene	$CHCl_3$	25	23.3	439	676	55
	Tetraphene	$CHCl_3$	25	10.7	497		55
	Pyrene	$CHCl_3$	25	18.3	500	1040	55
	Anthracene	$CHCl_3$	25	5.5	517	1416	55
	Perylene	$CHCl_3$	25	57.8	592	769	55
	Mesitylene	EtOAc	18	0.14 ± 0.03[c]			56
	Durene	EtOAc	18	0.46 ± 0.03[c]			56
	Pentamethylbenzene	EtOAc	18	0.62 ± 0.03[c]			56
	Hexamethylbenzene	EtOAc	18	1.24 ± 0.07[c]			56
	Triphenylene	MeCN	25	14.5 ± 0.4	390[f]	420 ± 90[f]	57
	Triphenylene	Me_2CO	25	24 ± 8	385[f]	348 ± 90[f]	57
	Triphenylene	THF[e]	25	18.3 ± 0.5	385[f]	300 ± 60	57
	Triphenylene	CH_2Cl_2	25	5.8 ± 0.2	415	1329 ± 24	57
	Pyrene	CH_2Cl_2	25	8.3 ± 0.3	505	1048 ± 25	57
	Benz[*a*]anthracene	CH_2ClCH_2Cl	33.5	4.3[g]			39
3,6-Dinitronaphthalene-1,8-dicarboxylic acid anhydride	Pyrene	$CHCl_3$	27.5	3.27 ± 0.10	510		27

[a] *Estimated from K_x using the relationship $K_c = vK_x$.*
[b] MCXA = methylcyclohexane.
[c] Room temperature.
[d] DABCO = diazobicyclo[2.2.2]octane.
[e] THF = tetrahydrofuran.
[f] Shoulder.
[g] Estimated from K in moles per kg of solution.

Despite there being very little positive evidence for termolecular complex formation involving anhydrides, the possibility remains. The results obtained from the other π-donor–π^*-acceptor systems indicate that, were termolecular complexes to be present but not allowed for, the formation constants and related parameters (such as ϵ or Δ_0) could be in error by as much as a factor of two. The data, summarized in Table 2, should be read in conjunction with this possible proviso.

As with other EDA complexes, the solvent has a very considerable effect on K. Solutions involving less polar solvents yield the more stable complexes. For example, for acenaphthene–tetrachlorophthalic anhydride at 20°C in carbon tetrachloride $K_c = 5.6 \pm 0.2$ l mol^{-1}, whereas in tetrahydrofuran $K_c = 0.5 \pm 0.1$ l mol^{-1} [38]. This is typical for weak, non-polar EDA complexes. Solvent competition can have large effects on the measured association constant. There is little doubt that this accounts for much of the difference between the K_c values of hexamethylbenzene–tetrachlorophthalic anhydride in *n*-hexane ($K_c = 34$ l mol^{-1}) and benzene ($K_c = 2.3$ l mol^{-1})[17]. Solvent competition does not account for the whole difference, however. Thus Nagy, Nagy and Bruylants[38] have estimated the effect of solvent competition in the acenaphthene–tetrachlorophthalic anhydride complexes. When allowance is made for this there are still significant differences in the association constants (Table 2). Internal pressure of the solvent and solvation of all of the solute species undoubtedly contribute to these differences. In addition, there is evidence that some species of the larger donor molecules, at least, do dimerize in solution[58]. Although this may not be extensive, it may be sufficient to cause serious misinterpretation of experimental observations.

Caze and Loucheux[48] have attempted to estimate directly the effect of complex formation between the acceptor and the solvent. However, their method includes measurements on solutions of high donor concentration (in one case, over 7M). In these circumstances deviations from ideal behaviour depend on more factors than simply solvent competition.

III. CRYSTAL STRUCTURES OF SOLID COMPLEXES

A. General

Crystal-structure determination by X-ray diffraction has been an important aspect of the study of π–π^* EDA complexes since Powell and his coworkers[59,60] established the fact that the intermolecular distance in such complexes was never much less than the van der Waals' distance, so establishing the relatively weak nature of the groud-state intermolecular bonding.

There have been several reviews of crystal structures of EDA complexes[61-63] The reader is referred also to the detailed account of the X-ray diffraction study of pyrene–pyromellitic dianhydride[64].*

The stoichiometry of the π-donor–anhydride complexes is usually 1:1 although other ratios have been reported, e.g. perylene and pyrene with pyromellitic

*Note: This section describes the structures *as obtained by X-ray diffraction methods*. N.m.r. studies by Fyfe and coworkers [C. A. Fyfe in *Molecular Complexes* (Ed. R. Foster), Elek Science, 1973, Chap. 5; C. A. Fyfe, D. Harold-Smith and J. Ripmeester, *J. Chem. Soc., Faraday II*, 72, 2269 (1976) and references therein] have shown that very considerable molecular motion occurs in many such solids.

dianhydride (PMDA)[56,65], pyrene with metallic trianhydride[66], and dibenz-[*a*,*h*]anthracene with PMDA[67]. In many such interacting species, the corresponding complexes of 1 : 2 stoichiometry are also known, as in the examples cited. To the author's knowledge, in the set of anhydride complexes structures have only been determined for complexes with 1 : 1 stoichiometry. The common feature of the crystal structures of 1 : 1 π-donor–π^*-acceptor complexes is the alternate arrangement of donor and acceptor molecules in stacks, all the molecules in a given stack lying parallel or near-parallel to one another, though not usually orthogonal to the stack direction. The angle between the normal to the average plane of the component molecules and the stack direction is called the stack angle. One effect of a finite stack angle is the lack of coincidence of the centres of the donor and acceptor molecules in the overlap diagram, usually represented by the molecular arrangement of one component of the complex projected normal to the mean plane of the other component. For a number of systems, successive molecules of one species do not occupy equivalent positions in a stack so that the repeat unit is –D–A–D–A– rather than –D–A– and the periodicity of the stack is ca 14Å rather than the more normal ca 7Å. Since crystals consist of three-dimensional arrays of the component molecules, the description as stacks of alternating donor and acceptor is only one view of the structure. Nevertheless, because of the model we have of an isolated donor–acceptor pair and the evidence that generally intrastack forces are stronger than interstack forces, except in cases where some other strong interaction, e.g. hydrogen bonding, occurs, the structures of π–π^*-EDA complexes are virtually always thought of as being made up of stacks of alternating D and A molecules.

Where comparative measurements have been made, molecular dimensions in condensed aromatic donors show no difference to the corresponding values in crystals of the pure donor. Although the same is approximately true for the acceptors, small deviations from planarity of the complexed anhydride are observed in some cases. In the case of the donor moiety the assessment of agreement is often limited by the relatively poor data for the crystalline uncomplexed donor, to the extent that for some condensed aromatic hydrocarbons at least, the crystal structures of complexes with acceptors probably yield more accurate molecular dimensions of the donor than the donor crystals alone can.

B. Specific Systems

1. Benzene – PMDA

Exploratory work by Boeyens and Herbstein[68] has enabled the unit cell dimensions and space group ($P2_1/a$) to be determined at room temperature. The complex is unstable. No further studies appear to have been made on this system.

2. Naphthalene – PMDA

From room-temperature determinations of unit cell dimensions and symmetry, Boeyens and Herbstein[68] have concluded that the structure is disordered. No phase changes were observed when the crystals were cooled to 100 K. *Average* positions of D and A molecules in the lattice yield the space group $C2/m$.

3. Anthracene – PMDA

Boeyens and Herbstein[69] have shown that this complex undergoes no phase change on cooling down to 100 K. They have concluded that there is no disorder at

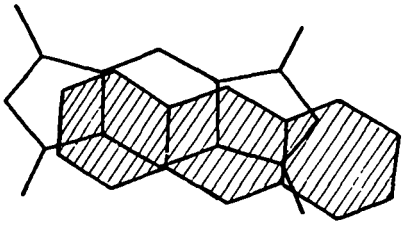


FIGURE 1. The molecular arrangement in anthracene–pyromellitic dianhydride seen in projection onto the plane of the anthracene molecule. Reproduced with permission from J. C. A. Boeyens and F. H. Herbstein, *J. Phys. Chem.*, 69, 2160 (1965).

room temperature. Observations including two-dimensional experiments at room temperature give a space group $P\bar{1}$. The molecules in identical stacks of alternate donor and acceptor molecules are typical of this class of complex. The mean intermolecular distance within a stack is 3.23Å. The overlap diagram is given in Figure 1.

4. Perylene – PMDA

A full three-dimensional structure analysis of this complex at room temperature has been described by Boeyens and Herbstein[69]. With space group $P2_1/a$, the stacks of alternate donor and acceptor lie along [010]. Typical of several PMDA complexes, the acceptor is twisted slightly into a centrosymmetrical form. The intermolecular distance within a stack is 3.33Å. The overlap diagram is given in Figure 2. No evidence of disorder was observed at room temperature although a phase change occurs on cooling. However, at low temperatures the crystals shattered so that no detailed structure could be obtained.

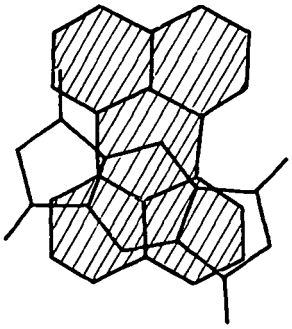


FIGURE 2. The molecular arrangement in perylene–pyromellitic dianhydride seen in projection onto the plane of the perylene molecule. Reproduced with permission from J. C. A. Boeyens and F. H. Herbstein, *J. Phys. Chem.*, 69, 2160 (1965).

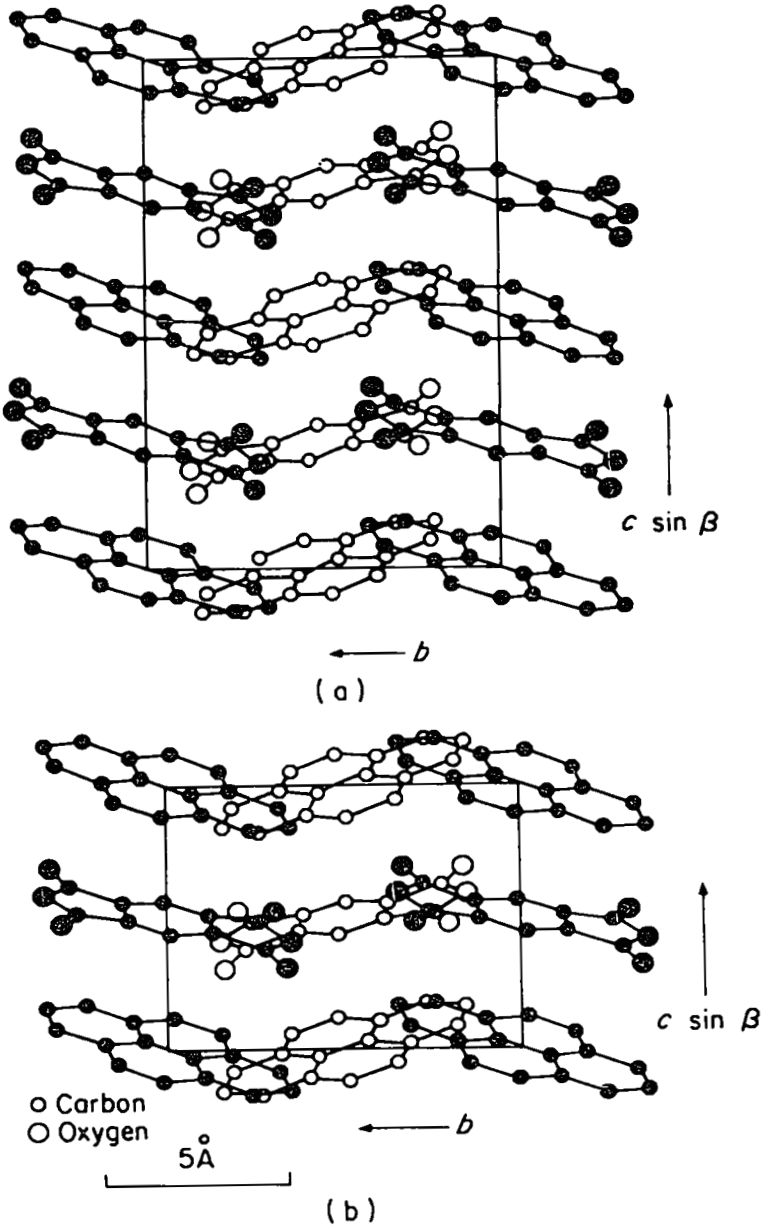


FIGURE 3. The molecular arrangement in pyrene–pyromellitic dianhydride seen in projection down [100] in (a) the low-temperature structure, (b) the room-temperature structure. In this figure and in Figure 4 the molecules whose centres lie at about half-way along the axis of projection are shown by open circles and those whose centres lie in the plane of the diagram by filled circles. Reproduced with permission from F. H. Herbstein and J. A. Snyman, *Phil. Trans. Roy. Soc.*, 264A, 635 (1969).

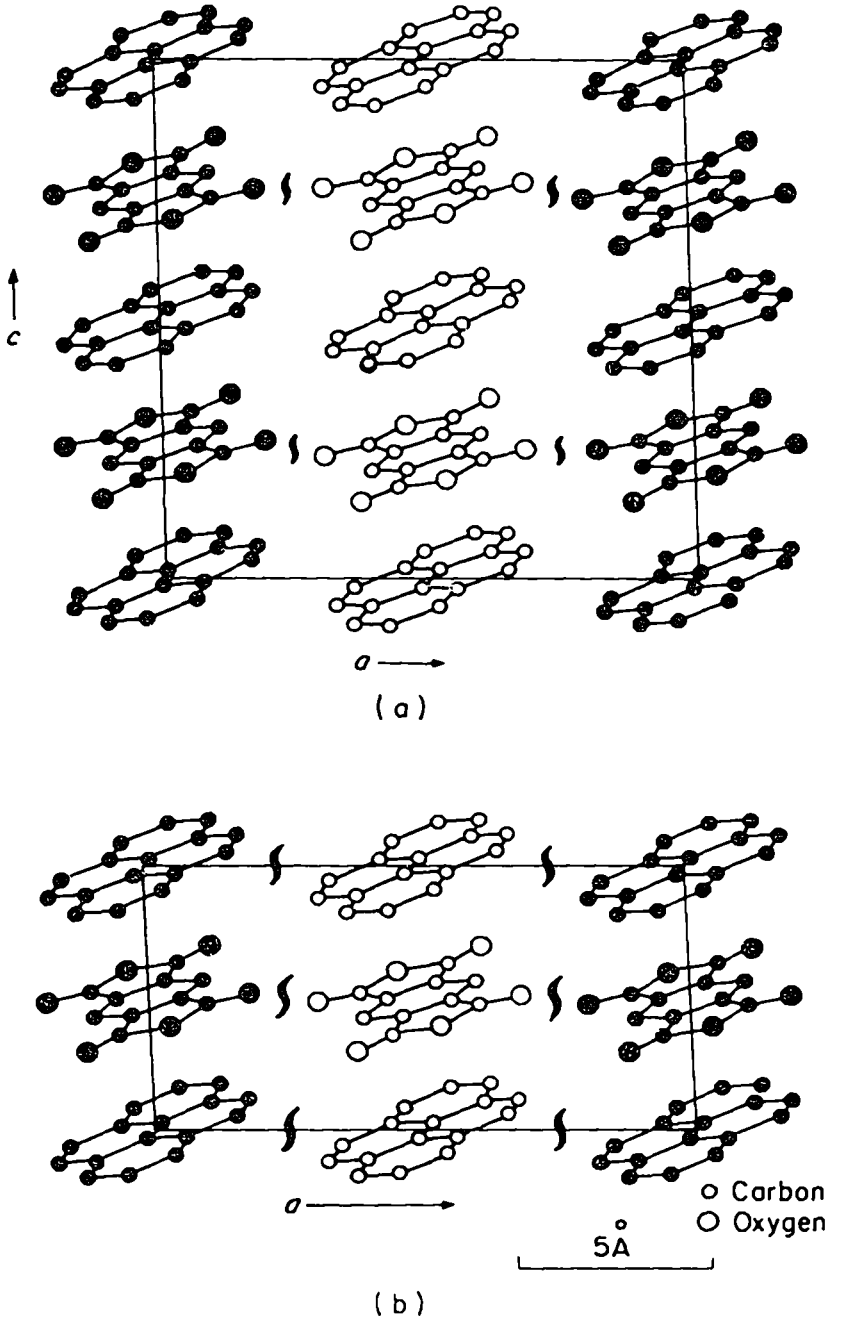
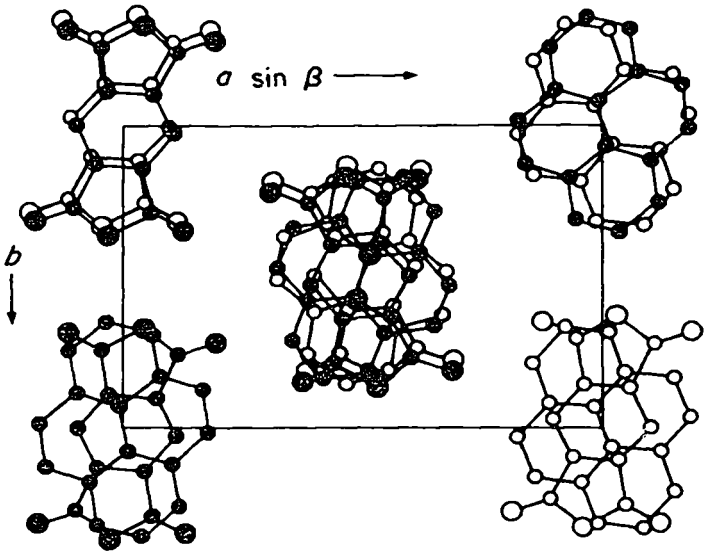
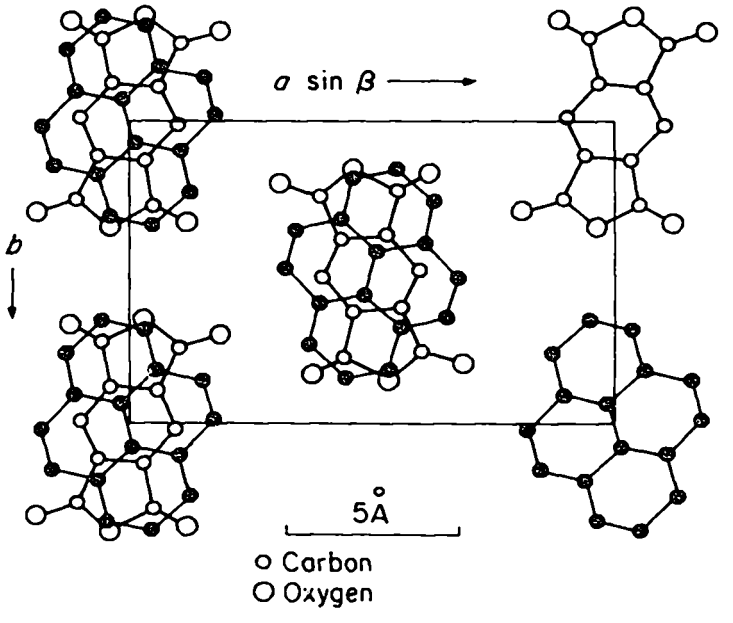


FIGURE 4. The molecular arrangement in pyrene–pyromellitic dianhydride seen in projection down [010] in (a) the low-temperature structure, (b) the room-temperature structure. Reproduced with permission from F. H. Herbstein and J. A. Snyman, *Phil. Trans. Roy. Soc.*, **264A**, 635 (1969).



(a)



(b)

5. *Pyrene – PMDA*

This system has been the subject of a very extensive and careful study by Snyman and Herbstein[64]. On cooling crystals of this complex down from room temperature they observed a disorder-to-order transition at about 200 K. They therefore proceeded to carry out a complete three-dimensional analysis of both structures. The disordered structure measured at 300K has the space group $P2_1/a$ whilst the ordered structure measured at 110 K has the space group $P2_1/n$. Comparison of the two structures down the three crystallographic axes is given in Figures 3–5. In the ordered structure the pyrene molecules alternate between two orientations, about 12° apart, with respect to the PMDA molecules. These latter molecules themselves have small displacements of alternate molecules with respect to the stack axis. The spacing between consecutive molecules in the stack also alternates (3.333Å and 3.296Å); there is a corresponding alternation in the angles between the mean planes of successive pairs of molecules, namely 1.3° and 0.0°. These differences are very small and when the intermolecular distances between specific atoms are considered there is no clear difference between the proximity of the donor on one side of an acceptor molecule and that of the donor on the other side of the same acceptor molecule; in other words there is no obvious 'pairing' of molecules in the stack.

The dimensions of pyrene obtained from this analysis agree well with those from determinations involving pure pyrene crystals. In the complex the PMDA molecule is slightly twisted into a centrosymmetrical form.

The overlap diagrams for successive donor–acceptor pairs in the low-temperature form are represented in Figure 6.

6. *Phenanthrene – PMDA*

This complex which forms crystals having a monoclinic space group $P2_1/c$ has been shown by Evans and Robinson[70] to have the typical structure of stacks of alternating phenanthrene and PMDA molecules. The adjacent molecules within the stack are nearly parallel. The shortest intermolecular distance within the stack is 3.36Å. The overlap diagram is given in Figure 7.

7. *Fluorene – PMDA*

The crystals have the space group $P2_1/c$ with stacks of alternating fluorene and PMDA molecules[71]. Half the fluorene molecules are reversed in orientation (Figure 8). The stacks are considerably staggered, the fluorene and PMDA molecules making angles of 44.98° and 38.69° respectively with the x axis. This is reflected in the overlap diagram (Figure 9).

FIGURE 5. The molecular arrangement in pyrene–pyromellitic dianhydride seen in projection down [001] in (a) the low-temperature structure, (b) the room-temperature structure. In (a) the pyromellitic dianhydride molecules near ¼c are represented by closed-circle models and those near ¾c by open-circle models. For the sake of clarity two molecules have been left out at each corner of this projection. In (b) one pyrene and one pyromellitic dianhydride molecule have been left out for clarity. Reproduced with permission from F. H. Herbstein and J. A. Snyman, *Phil. Trans. Roy. Soc.*, 264A, 635 (1969).

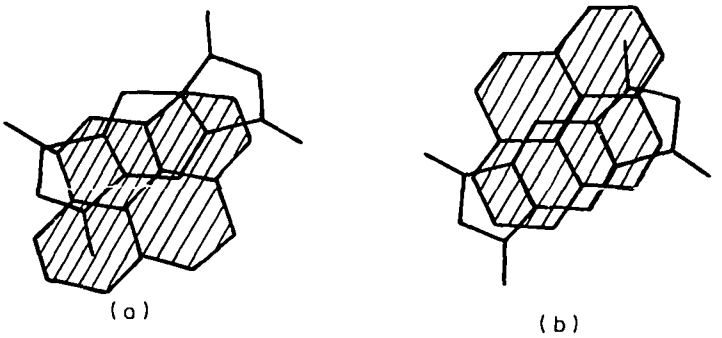


FIGURE 6. The molecular arrangement in pyrene–pyromellitic dianhydride in the low-temperature structure as seen in projection normal to their molecular planes. For clarity two drawings are shown: (a) the molecular arrangement of pyrene$^{(1)}$ and pyromellitic dianhydride$^{(1)}$ in projection normal to the plane through pyrene$^{(1)}$, and (b) the molecular arrangement of pyromellitic dianhydride$^{(1)}$ and pyrene$^{(2)}$ in projection normal to the plane through pyrene$^{(2)}$. The superscript numbers indicate pyrene molecules in the alternative orientations with respect to the pyromellitic dianhydride molecules (see text). Reproduced with the permission from F. H. Herbstein and J. A. Snyman, *Phil. Trans. Roy. Soc.*, 264A, (1969).

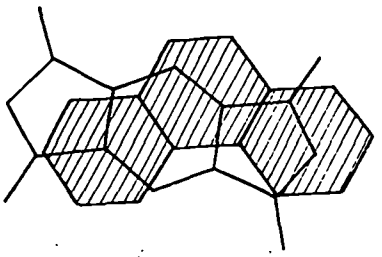


FIGURE 7. The molecular arrangement in phenanthrene–pyromellitic dianhydride viewed perpendicular to the plane of the molecules. Reproduced with permission from D. L. Evans and W. T. Robinson.

8. Thianthrene – PMDA

This structure has the space group $P\bar{1}$[72] with stacks of alternating thianthrene and PMDA molecules, the latter aligning themselves parallel to each of the two planes of the thianthrene in an alternating fashion as is shown in Figure 10. (The angle between the two 'wings' of thianthrene is 130.08°.) The average distance between adjacent donor and acceptor molecules in a stack is 3.51Å, not very different from the values observed in systems where both molecular species are effectively planar.

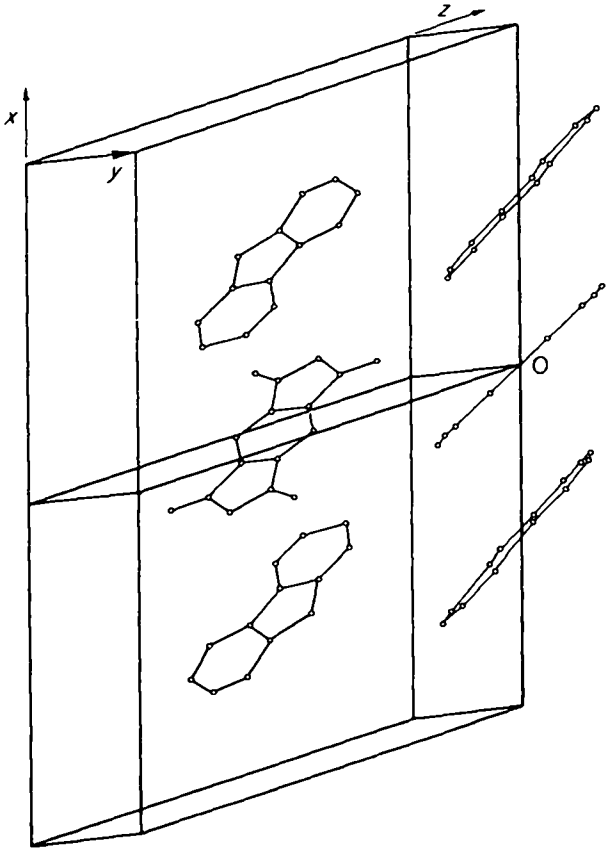


FIGURE 8. The molecular arrangement in fluorene–pyromellitic dianhydride viewed parallel to the plane of one set of molecules. Reproduced with permission from D. L. Evans and W. T. Robinson.

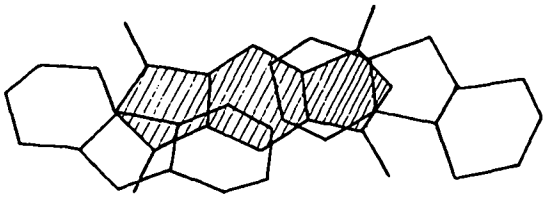


FIGURE 9. The molecular arrangement in fluorene–pyromellitic dianhydride as seen in projection normal to their molecular planes. Reproduced with permission from D. L. Evans and W. T. Robinson.

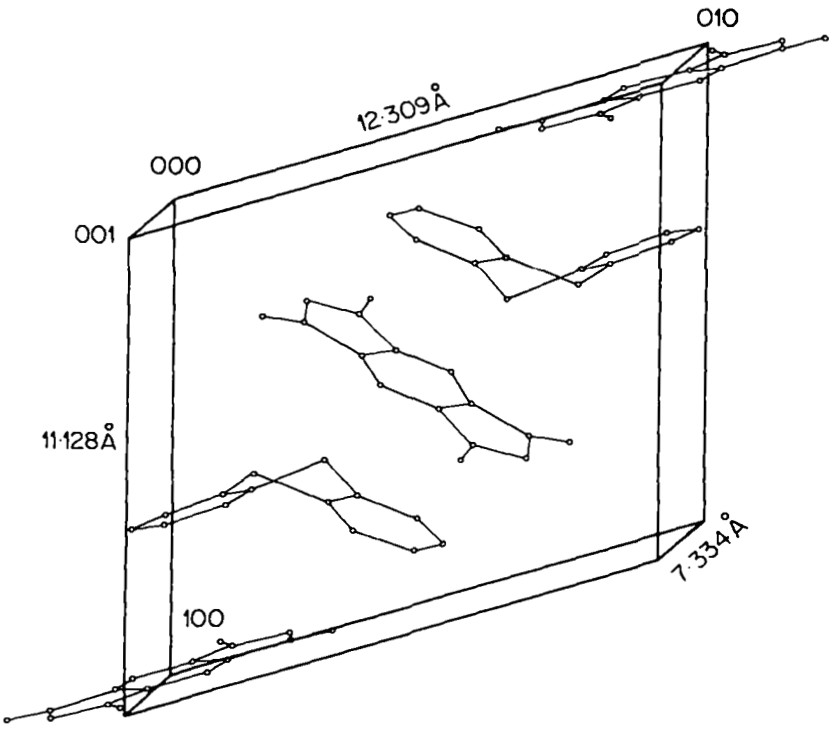


FIGURE 10. The molecular arrangement in thianthrene–pyromellitic dianhydride showing the arrangement in a unit cell. Reproduced with permission from D. L. Evans and W. T. Robinson.

9. *Benz[a]anthracene – PMDA*

The room-temperature structure of this complex[39] has space group $P2_1/a$. The alternation effects of the distances between mean planes of successive molecules in a stack (3.37Å and 3.39Å) and the corresponding angles between the mean planes (4.7° and 3.4°) are small as in the case of pyrene–PMDA described above. The notion of 'mean plane' has less significance for benz[*a*]anthracene complexes than for many other condensed aromatic hydrocarbon donor–π^*-acceptor complexes, however, because of the considerable deviation from planarity of the benz[*a*]-anthracene moiety. Problems of sample preparation make a refined structure determination of benz[*a*]anthracene itself difficult to achieve, but there is little doubt that the molecule is non-planar, due primarily to the steric hindrance of the hydrogen atoms attached to $C_{(1)}$ and $C_{(12)}$.

Some deviation from planarity has also been detected in the acceptor molecule though, to date, this has not been clearly shown to give rise to a centrosymmetric system as in the case of some other PMDA complexes.

There is a much larger difference in the orientation of one donor molecule with a given acceptor molecule and the next donor molecule with the *same* acceptor molecule (Figure 11) than in the case for the ordered pyrene–PMDA structure (Figure 6).

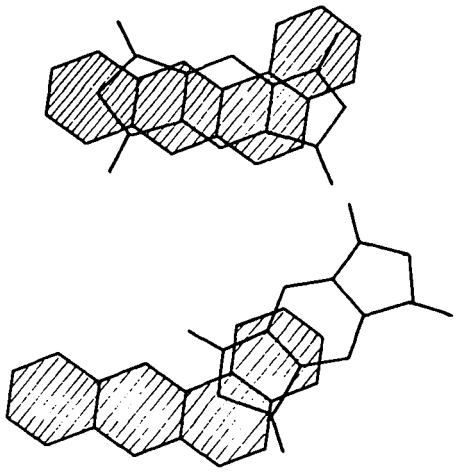


FIGURE 11. The molecular arrangement in benz[*a*]anthracene–pyromellitic dianhydride showing the projections of a pyromellitic dianhydride molecule onto the mean plane of each of two successive benz-[*a*]anthracene molecules in a stack. Reproduced with permission from R. Foster, J. Iball, S. N. Scrimgeour and B. C. Williams, *J. Chem. Soc., Perkin II*, 682 (1976).

10. trans-Stilbene — PMDA

Kodama and Kumakura[73] report that this complex crystallizes in the space group $P2_1/c$. In the complex the donor moiety is non-planar, the central ethylene group making angles of 11.5° with the plane of each phenyl group. By comparison, an early structure determination of *trans*-stilbene itself by Robertson and Woodward[74] showed that in that situation there are two kinds of molecule with corresponding torsional angles of ca 3° and ca 10°. The complexed acceptor deviates from planarity by about the same small degree as does PMDA in the pyrene

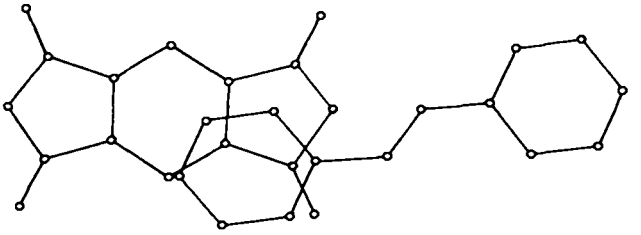


FIGURE 12. The molecular arrangement of *trans*-stilbene–pyromellitic dianhydride showing the projection of a *trans*-stilbene molecule onto the mean plane of a molecule of pyromellitic dianhydride. Reproduced with permission from T. Kodama and S. Kumakura, *Bull. Chem. Soc. Japan*, 47, 1081 (1974).

and perylene complexes (see above). The average interplanar donor–acceptor separation is 3.59Å (the shortest intermolecular distance is 3.49Å). The overlap diagram is given in Figure 12.

11. Anthracene–pyromellitic dithioanhydride

This complex[75] crystallizes in the space group $P2_1/c$. The average intermolecular separation within the stacks is 3.41Å, significantly larger than 3.23Å for the corresponding PMDA complex and probably a result of the larger van der Waals radius of the sulphur atom. The overlap diagram (Figure 13) indicates a somewhat more staggered packing than for anthracene–PMDA (Figure 1).

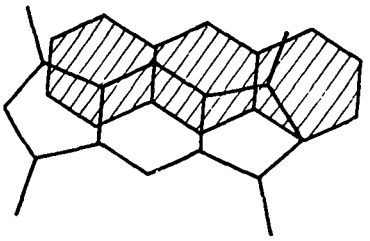


FIGURE 13. The molecular arrangement of anthracene–pyromellitic dithioanhydride showing the superimposition of two neighbouring molecules in a stack. Adapted from I. V. Bulgarovskaya, E. M. Smelyanskaya, Yu. G. Fedorov and Z. V. Zvonkova, *Sov. Phys. Crystallogr.*, **19**, 157 (1974).

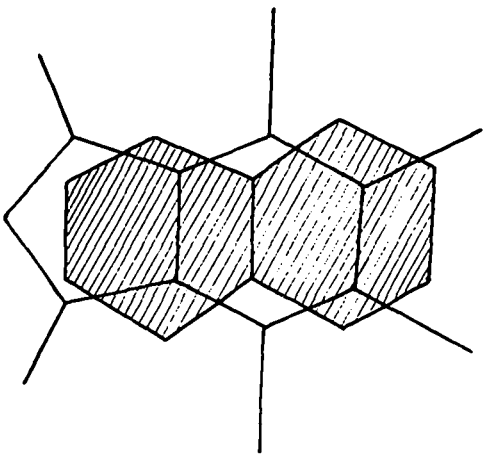


FIGURE 14. The molecular structure of naphthalene-d_8–tetrachlorophthalic anhydride at 120 K, showing the superposition of two neighbours in a stack. Adapted from A. K. Wilkerson, J. B. Chodak and C. E. Strouse, *J. Amer. Chem. Soc.*, 97, 3000 (1975).

12 Naphthalene-d_8—tetrachlorophthalic anhydride

Strouse and his coworkers[76] have determined the structure of this complex at 120 K. It is the first naphthalene EDA complex to be studied which has an ordered structure. The structural parameters for the two molecular species within the complex are, within experimental error, identical with the corresponding parameters of the two separate components, TCPA as crystals, and napthalene both as crystals and as vapour. The D and A molecules lie vertically parallel in the infinite stacks. The intermolecular separation within the stack is 3.33Å. The overlap diagram is given in Figure 14.

IV. ELECTRONIC SPECTRA

A. Absorption Spectra

The intermolecular charge-transfer absorption band(s) of certain EDA complexes characterizes them as 'charge-transfer complexes'. From the original Mulliken theory, the following relationship between the energy of the charge-transfer transition (E_{CT}), the appropriate ionization potential of the donor (I_D) and the appropriate electron affinity of the acceptor (EA_A) may be derived[77,78]:

$$E_{CT} = I_D - EA_A + C_1 - \frac{C_2}{I_D - EA_A + C_1} \tag{5}$$

where C_1 and C_2 are approximately constant for a given acceptor. Since the energy E_{CT} corresponds to a transition under Franck–Condon conditions, the ionization potentials and electron affinities should be the vertical, as opposed to the adiabatic energies. Where a single charge-transfer band is observed, this corresponds to a transition from the highest-filled orbital of the donor to the lowest-unfilled orbital of the acceptor, that is, the lowest ionization potential of the donor and electron affinity of the acceptor are involved. Some values of charge-transfer maxima for anhydride complexes are given in Table 2 and 3. Typical of weak EDA complexes, these transitions are relatively insensitive to solvent change even when a considerable alteration in solvent polarity is involved (see Table 3).

Although the theoretical relationship between E_{CT} and I_D for a series of complexes with a given acceptor is hypobolic (equation 5), in practice a good linear correlation is generally observed. Lack of a wide range of reliable electron affinity values have made similar comparisons between E_{CT} and EA_A hitherto impossible. However, properties of the electron acceptor related to electron affinity have been used to demonstrate such a linear relationship. The property most often used has been the half-wave reduction potential of the acceptor in an aprotic solvent such as acetonitrile, usually against a standard calomel electrode[81-84]. Comparisons of these reduction potentials as measures of electron affinity are made on the assumption that the difference in solvation energy between the electron acceptor and its negative ion is independent of the particular acceptor, which cannot be strictly correct.

Such are the difficulties in obtaining electron affinity values for molecules with relatively high affinity values, that various workers have used the energies of the intermolecular charge-transfer transitions (E_{CT}) of the molecules with electron donors in order to estimate the EA_A values. Since such estimates will only provide the energy differences between EA_A values, some standard electron affinity value

TABLE 3. Frequencies (ν_{CT}) of maxima of intermolecular charge-transfer bands[a]

Acceptor[b]	Donor	Solvent	ν_{CT}(cm^{-1} × 10^{-3})[c]	Reference
TCPA	Hexamethylbenzene	*n*-C_6H_{14}	26.1	17
TCPA	Hexamethylbenzene	CCl_4	25.6	17
TCPA	Hexamethylbenzene	CH_2ClCH_2Cl	25.85	54
PMDA	Benzene	CCl_4	33.6	79
	Toluene	CCl_4	30.3 34.0	79
	o-Xylene	CCl_4	28.9 33.3	79
	m-Xylene	CCl_4	28.6 33.2	79
	p-Xylene	CCl_4	28.1 32.5	79
	Mesitylene	CCl_4	27.3 33.1	79
	1,2,4-Trimethylbenzene	CCl_4	27.0 32.9	79
	Durene	CCl_4	25.6 28.6 32.6	79
	Pentamethylbenzene	CCl_4	24.4 29.0 32.1	79
	Hexamethylbenzene	CCl_4	23.0 28.1 31.7	79
	Anisole	EtOAc	27.1	80
	Naphthalene	AcOEt	25.8	80
	Anthracene	AcOEt	20.9	80
	Pyrene	AcOEt	21.3	80
	Chrysene	AcOEt	23.1	80
	Phenanthrene	AcOEt	25.0	80
	trans-Stilbene	AcOEt	24.2	80
	Naphthalene	$CHCl_3$	24.2	57
	Anthracene	$CHCl_3$	19.3	57
	Phenanthrene	$CHCl_3$	24.6	57
	Fluorene	$CHCl_3$	23.1	57
	Chrysene	$CHCl_3$	22.8	57
	Pyrene	$CHCl_3$	20.0	57
	Perylene	$CHCl_3$	16.9	57
	Triphenylene	$CHCl_3$	24.1	57
	Fluoranthene	$CHCl_3$	23.8	57
	Tetraphene	$CHCl_3$	20.1	57

[a] Values for some other systems are listed in Table 2.
[b] TCPA = tetrachlorophthalic anhydride; PMDA = pyromellitic dianhydride.
[c] These are the maxima reported: there may be others.

has to be taken. It was in this way that two sets of electron affinity values both derived from E_{CT} values were established. Bately and Lyons[85] based theirs on a value of 1.8 eV for the *EA* of the iodine molecule. Briegleb[86] based his on a value of 1.37 eV for the *EA* of chloranil (tetrachloro-*p*-benzoquinone). Unfortunately, the two sets are not consistent with each other: on Bately and Lyons' scale chloranil has an *EA* of 2.59 ± 0.17 eV.

However, there have been determinations of the electron affinities of some strong electron acceptors by what may be called 'direct methods', for example the magnetron method[87,88], although even here there were in the development of the technique some uncertainties regarding some of the results. Recently Chen and Wentworth[89] have reestimated the *EA* values of a considerable number of compounds based on a linear correlation of E_{CT} with I_D for a given acceptor, and of E_{CT} with EA_A for a given donor, and adjusted the EA_A scale to give the best fit for certain EA_A values, obtained from independent 'direct' methods. This has provided a reasonably consistent set of *EA* values. Values for a number of anhyd-

TABLE 4. Electron affinity values of some anhydrides as evaluated by Chen and Wentworth[89]

Anhydride	*EA* (eV)
Maleic anhydride	1.33
Dichloromaleic anhydride	1.60
Phthalic anhydride	1.30
Tetrabromophthalic anhydride	1.72
3,6-Dichlorophthalic anhydride	1.50
Tetrachlorophthalic anhydride	1.72
4-Nitrophthalic anhydride	1.80
3,5-Dinitrophthalic anhydride	2.32
Pyromellitic dianhydride	2.04
Dibromopyromellitic dianhydride	2.23
Naphthalene-1,8-dicarboxylic anhydride	1.37
2,3-Pyridine dicarboxylic anhydride	1.30
3-Nitronaphthalene-1,8-dicarboxylic anhydride	1.79
Homophthalic acid anhydride	1.33
Mellitic trianhydride	2.38
Naphthalene-1,4,5,8-tetracarboxylic dianhydride	2.28

rides, together with those of some other electron acceptors for comparison, are given in Table 4.

Although it is often convenient to consider EDA structures in terms of equations (1) and (2), Murrell[90] pointed out that the absorption intensities of the intermolecular transitions cannot be rationalized in terms of this simple model. He suggested that varying degrees of energy borrowing occur, for example from locally excited states of the donor (D*, A) and of the acceptor (D, A*). There may also be contributions from states in which an acceptor donates an electron to the donor, i.e. back-donation (D^-–A^+). Equation (1) may therefore be amended thus:

$$^1\psi_N(DA) = a^1\psi(D, A) + \Sigma b^1\psi(D^+ - A^-) + \Sigma c^1\psi(D^- - A^+) + \Sigma d^1\psi(D^*, A) + \Sigma e^1\psi(D, A^*) \ldots \quad (6)$$

The first singlet excited state of the complex will then be:

$$^1\psi_E(DA) = a^{*1}\psi(D, A) + \Sigma b^{*1}\psi(D^+ - A^-) + \Sigma c^{*1}\psi(D^- - A^+) + \Sigma d^{*1}\psi(D^*, A) + \Sigma e^{*1}\psi(D, A^*) \ldots \quad (7)$$

Recently Deperasinska[91] has calculated the absorption spectra and intensities of the transitions for the complex hexamethylbenzene–pyromellitic dianhydride based on such a mixing of locally-excited and intermolecular charge-transfer states. Comparison with experimental observations indicates that, although the calculated mixing is not large, the actual measured changes in intensity can be quite significant. This has been explained in terms of interaction between locally-excited configurations as a result of complex formation.

Mataga and his coworkers[92] have measured the singlet–singlet absorption bands of singlet excited toluene–pyromellitic dianhydride complex. The spectrum corresponds closely to the superposition of the absorption bands of the acceptor anion and the donor dimer cation. This suggests that in this complex with a liquid donor (and there is similar evidence from other examples) the fluorescent state can involve

a 2 : 1 complex of donor and acceptor. Since it is the donor dimer-type absorption which is observed, it is suggested that this excited trimer is $D_2^+A^-$ rather than $(D^+-A^- \ldots D \leftrightarrow D \ldots A^--D^+)$, a conclusion consistent with the high dipole moment of the fluorescent state[93].

In the absorption spectra of single crystals of anthracene–pyromellitic dianhydride at low temperature, sharp structure is observed consisting of a strong line with a number of satellites[94]. This has been assigned to a zero-phonon transition together with vibronic interaction. A similar effect is seen in fluorescence emission[94]. A second zero-phonon line induced by a static electric field has also been observed[95].

B. Fluorescence Spectra

The position of the fluorescence band for the transition $^1\psi_E(DA) \rightarrow {}^1\psi_N(DA)$ mirrors the corresponding lowest energy absorption band as expected. Such emission was first observed in glass matrices at low temperatures[96-99], but was also detected in mobile solution at room temperature[17]. Since then other systems have been described[79,100]. Some values are given in Table 5.

For the pyromellitic dianhydride complexes of the series of methylbenzenes from toluene to hexamethylbenzene, in carbon tetrachloride solution at room temperature, the relationship between absorption and fluorescence emission is clearly seen (Figure 15). The Stokes' shifts are expected to be large in view of the

TABLE 5. Fluorescence maxima (ν_F) for some EDA complexes

Acceptor	Donor	Solvent	T (K)	ν_F(cm^{-1} x 10^3)	Reference
Tetrachlorophthalic anhydride	Durene	PEI[a]	83	21.7	97
	Hexamethylbenzene	PEI[a]	83	20.0	97
	Naphthalene	PEI[a]	83	22.5	97
	Anthracene	PEI[a]	83	19.0	97
	Phenanthrene	PEI[a]	83	21.5	97
	Benz[*a*]anthracene	PEI[a]	83	19.6	97
Pyromellitic dianhydride	Benzene	CCl_4	room	24.8	79
	Toluene	CCl_4	room	22.4	79
	o-Xylene	CCl_4	room	20.8	79
	m-Xylene	CCl_4	room	20.6	79
	p-Xylene	CCl_4	room	20.0	79
	Mesitylene	CCl_4	room	20.3	79
	1,2,4-Trimethylbenzene	CCl_4	room	19.2	79
	Durene	CCl_4	room	18.7	79
	Pentamethylbenzene	CCl_4	room	18.2	79
	Hexamethylbenzene	CCl_4	room	17.2	79
	Hexamethylbenzene	CCl_4	room	16.9	100
	Hexamethylbenzene	CXA[b]	room	17.5	100
	Hexamethylbenzene	*n*-Bu_2O	room	16.5	100
	Naphthalene	CCl_4	room	18.9	100
Tetrachlorophthalic anhydride	Hexamethylbenzene	CCl_4	room	19.0	100
	Hexamethylbenzene	CCl_4	room	18.6	17
	Hexamethylbenzene	*n*-Bu_2O	room	18.8	100
	N-Phenylcarbazole	CCl_4	room	17.4	100
	N-Phenylcarbazole	*n*-Bu_2O	room	17.1	100

[a] PEI = propyl ether + isopentane.

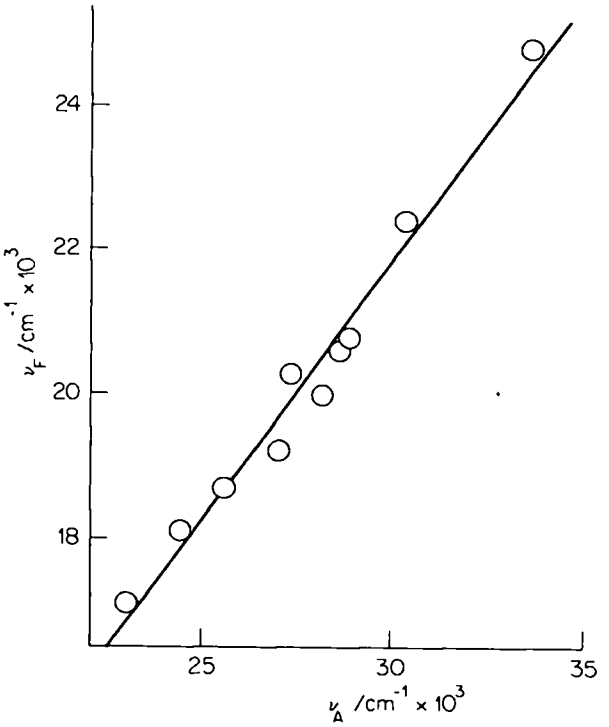


FIGURE 15. A plot showing the relationship between the frequencies of the fluorescence band and the corresponding absorption band for a series of methylbenzene–pyromellitic dianhydride complexes in carbon tetrachloride. Data from Reference 79.

differences between the Franck–Condon excited state, which will have largely the geometry and solvent orientation of the ground state, and the equilibrium excited state. The Stokes' shifts decrease with increasing donor strength throughout this series. Rosenberg and Eimutis[79] suggested that the shifts might be a measure of the difference in intermolecular separation of D and A between the $^1\psi_N(DA)$ and $^1\psi_E(DA)$ states, and that it is the lessening of the ground-state intermolecular distance with increasing donor strength which reduces the difference and accounts for the trend in the Stokes' shift. The fluorescence yields decrease throughout this series[101]. The fluorescence quantum yield also decreases with increasing solvent polarity, probably as a result of increased solvent-induced changes in the structure of the equilibrium excited state[102]. In sufficiently polar solvents fluorescence ceases and dissociation into solvent-separated ions becomes important.

Changes in the fluorescence spectra of the hexamethylbenzene, pyrene and anthracene complexes of tetrachlorophthalic anhydride with pressure were studied by Offen and Studebaker[103]. Whereas the absorption band is shifted by ~1500 cm^{-1} to the red at 25 kbar, the fluorescence spectra show only ~500 cm^{-1} shift at 30 kbar. When solvent effects have been taken into account, the observations are consistent with the generally accepted view that in the potential energy curve, $U(R)$, for the first excited state dU/dR is greater than the corresponding slope in the ground state[104].

TABLE 6. *Phosphorescence maxima (ν_P) and lifetimes (τ) for some EDA complexes*[a]

Acceptor	Donor	Phase or solvent	T (K)	ν_P(cm^{-1} x 10^3)	τ (sec)	Reference
Phthalic anhydride	Mesitylene	EI[b]	77	22.7(m)		110
	Durene	EI[b]	77	22.4(m)	0.78	110
	Hexamethylbenzene	EI[b]	77	20.9(m)	0.3	110
Dichlorophthalic anhydride	Durene	PEI[c]	83	21.37(m)	0.35	106, 107
	Durene	crystal	83		0.26	107
	Hexamethylbenzene	PEI[c]	83		0.095	106, 107
	Hexamethylbenzene	crystal	83		0.018	106, 107
	Naphthalene	PEI[c]	83	21.37(00)	2.1	106, 107
	Naphthalene	crystal	83		0.049	106, 107
	Phenanthrene	PEI[c]	83	21.65(00)	3.0	106, 107
	Phenanthrene	crystal	83		0.41	107
	Coronene	crystal	83	16.83(00)	1.05	106, 107
Tetrachlorophthalic anhydride	Durene	PEI[c]	83	19.70(m)	0.25	107
	Durene	crystal	83	19.60(m)	0.0020	107
	Durene	EI[b]	77	20.0(m)	0.25	110
	Hexamethylbenzene	PEI[c]	83		0.0085	106, 107
	Hexamethylbenzene	crystal	83		0.0011	106, 107
	Hexamethylbenzene	EI[b]	77	20.2(m)	0.004	110
	Mesitylene	EI[b]	77	20.2(m)		110
	Naphthalene	PEI[c]	83	21.30(00)	1.65	106, 107
	Naphthalene	crystal	83	19.00(00)	0.45	106
	Naphthalene	PE[d]	100	21.3(00)	1.3	108

	Anthracene	PEI[c]	83		0.04	107
	Phenanthrene	PEI[c]	83	21.55(00)	1.8	106
	Phenanthrene	crystal	83	19.50	0.25	107
	Phenanthrene	PE[d]	100	21.6(00)	1.1	108
	Benz[*a*]anthracene	PEI[c]	83	16.80(00)	0.41	107
Tetrabromophthalic anhydride	Durene	PEI[c]	83		0.0095	106, 107
	Durene	crystal	83		0.0012	106, 107
	Hexamethylbenzene	PEI[c]	83		0.0047	106, 107
	Hexamethylbenzene	crystal	83		0.001	106, 107
	Naphthalene	PEI[c]	83	21.20(00)	0.29	106, 107
	Naphthalene	crystal	83		0.029	106, 107
	Anthracene	crystal	83		0.16	107
	Phenanthrene	PEI[c]	83	21.18(00)	0.36	106, 107
	Phenanthrene	crystal	83		0.019	107
	Coronene	crystal	83	17.05(00)		106
Pyromellitic dianhydride	Mesitylene	EI[b]	77	20.0(m)		110
	Durene	EI[b]	77	20.3(m)		110
	Hexamethylbenzene	EI[b]	77	19.8(m)		110
	Naphthalene	PE[d]	100	21.3(00)		108
	Anthracene	crystal	1.6	15.42(00)	0.06	109

[a] Taken from S. Nagakura in *Excited States*, Vol. 2 (Ed. E. C. Lim), Academic Press, New York, San Francisco and London, 1975, p. 321.

[b] EI = ethyl ether + isopentane.

[c] PEI = proyl ether + isopentane.

[d] PE = *n*-propyl ether.

C. Phosphorescence Spectra

Phosphorescence has been observed for a number of anhydride complexes in solid matrices at low temperatures[105-110]. (Table 6). In the majority of cases the emissions are very similar to the phosphorescence of the corresponding donor. Eisenthal[111] showed that the triplet–triplet absorption of the tetrachlorophthalic anhydride complexes of perdeuteronaphthalene and perdeuterophenanthrene corresponds to transitions within the donor moieties of the complexes (see also Briegleb and Schuster[114,115]). However, Iwata, Tanaka and Nagakura[110] showed that phosphorescence characteristic of a charge-transfer triplet state could be observed in suitable complexes including those of pyromellitic dianhydride, tetrachlorophthalic anhydride and phthalic anhydride with various methylbenzenes.

Measurements of the polarization of the phosphorescence spectra of methylbenzene complexes of tetrachlorophthalic anhydride and phthalic anhydride indicate that the charge-transfer phosphorescence spectra are polarized normal to the molecular plane[116].

Matsumoto, Nagakura and Hayashi[117] have measured the triplet–triplet absorption spectra of the tetrachlorophthalic anhydride and phthalic anhydride complexes and also the e.s.r. of the lowest triplet states of tetrachlorophthalic anhydride and its complexes with the donors durene, mesitylene, toluene and benzene. The charge-transfer character of the lowest triplet states of these complexes is estimated to be 80, 46, 36 and 26% respectively. The lowest triplet states of the complexes of phthalic anhydride with mesitylene and toluene were found to have the character of the locally excited acceptor.

Gronkiewicz[118] has argued that in the case of hexamethylbenzene–tetrachlorophthalic anhydride the long-lived emission observed at low temperatures is in fact phosphorescence and not delayed fluorescence. This is despite the fact that the observed prompt fluorescence is at the same position as the long-lived emission since, when the temperature is increased from 98 K to 127.5 K, there is a large shift of nearly 40 nm in the position of the latter band.

V. CHEMICAL REACTIONS INVOLVING EDA COMPLEXES

A. Thermal Reactions

Some electron donor–acceptor systems not only immediately form EDA complexes but also more slowly form new species by irreversible chemical reaction. The EDA complex initially formed may be observed to disappear slowly. The question is whether the complex is a step on the overall reaction path or whether the formation of the complex is a side-equilibrium of the reactants[119-122]. Very often the two processes are kinetically indistinguishable as in the simple scheme:

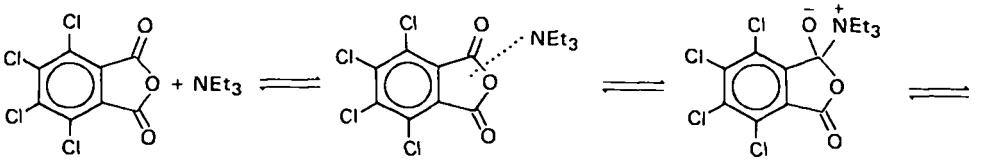
$$D + A \underset{}{\overset{K}{\rightleftharpoons}} DA \xrightarrow{k_a} \text{products} \tag{8}$$

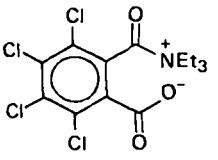
and

$$DA \overset{K^{-1}}{\rightleftharpoons} D + A \xrightarrow{k_b} \text{products} \tag{9}$$

With this in mind Nagy, Nagy and their coworkers[49,53,122,123] have sought other evidence to determine the possible involvement of EDA complexes in reactions of anhydrides with various tertiary amines including pyridine. In these reactions there

is good evidence for the initial formation of EDA complexes, some properties of which are listed in Table 1. The final products are zwitterions and there is evidence for 'tetrahedral' intermediates. For example in the reaction of tetrachlorophthalic anhydride with triethylamine[53] 2 is formed via 1





(2)

Pseudo first-order rate constants (k_1') were obtained by measuring the change in absorbance of the yellow EDA complex with time. For solutions containing large concentrations of amine [D] compared with anhydride, for the reaction to proceed by the EDA complex (equation 8) we may write:

$$k_1' = \frac{k^b K[D]}{1 + K[D]} \tag{10}$$

whereas if the EDA complex is only formed in a side-equilibrium then we must write:

$$k_1' = \frac{k^a[D]}{1 + K[D]} \tag{11}$$

When the solvent for the reaction was changed, no correlation of log k^a with the solvent parameter S^M was observed[124], whereas there was a moderate correlation of log k^b with S^M. The authors suggest that, in view of the probably specific interactions by some solvents, the level of consistency with scheme is acceptable. Other systems studied by Nagy, Nagy and Bruylants[53] include reactions of other bases such as 1,4-diaza[2.2.2]bicyclooctane (DABCO), pyridine and dimethylaniline. The anhydrides include 3-nitro-, 4-nitro-, 3,5-dinitro- and 3,6-dichlorophthalic anhydride, and 1,8-naphthalic anhydride[49]. In the reaction of 3,5-dinitrophthalic anhydride with pyridine, formation of the tetrahedral intermediate was assumed to occur not only by direct conversion of the EDA complex, but also in a separate, base-catalysed reaction of the initial reactants, analogous to the kinetic scheme proposed by Rappoport and Horowitz[125] for the reaction of tetracyanoethylene with *N,N*-dimethylaniline. The addition of another electron donor to the amine–anhydride reaction lowers the rate of reaction. Thus in the reaction of 3,5-dinitrophthalic anhydride with pyridine to which acenaphthene has been added, both free anhydride and anhydride complexed with acenaphthene react, the latter more slowly[48]. The initial step for the former process is the formation of the

1 : 1 EDA complex between anhydride and pyridine, whilst it is proposed that the anhydride–acenaphthene complex forms a 1 : 1 : 1 ternary complex, acenaphthene:3,5-dinitrophthalic anhydride:pyridine.

B. Photochemical Reactions

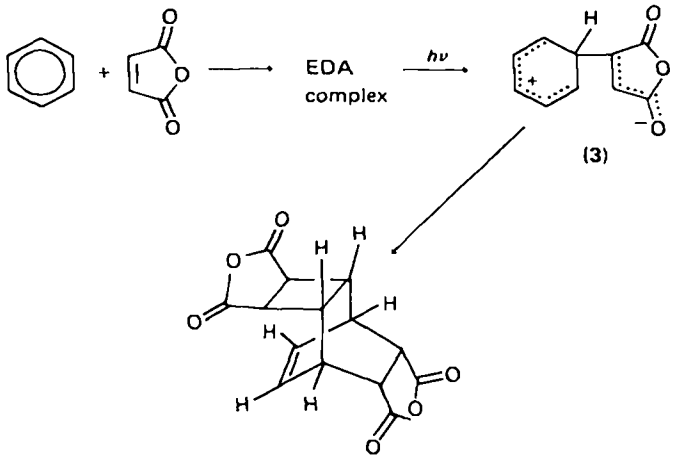
Mechanisms of a number of photochemical reactions involving electron donors and anhydrides which proceed through excited EDA complexes have been proposed[126,127]. The evidence to substantiate such a reaction pathway varies. Apart from those systems in which excitation is from a stable ground state of an EDA complex, there is an increasing number of photochemical reactions which involve excimers (excited-state complexes which have no stable ground state). Furthermore, it cannot be supposed that when a triplet-sensitizer such as benzophenone is added, the mechanism will still necessarily demand the involvement of an excited EDA complex.

Perhaps the simplest photochemical reaction which EDA complexes may undergo is photoionization. Several aspects of such processes for various anhydride complexes have been demonstrated. Thus Ottolenghi and his coworkers[128] irradiated the mesitylene–pyromellitic dianhydride complex in 2 : 1 ether–isopentane solutions at various temperatures down to 77 K. The energy of the radiation corresponded to the charge-transfer absorption band. Correlated measurements of flash absorption and emission were made. At sufficiently low temperatures the growth of an absorption, due to the acceptor anion, could be observed. At the same time the phosphorescence emission from the triplet state of the complex was measured. Both processes are first order and have a common rate constant of $\sim 800\ sec^{-1}$ at 117 K. Both processes are sensitive to molecular oxygen. These observations are consistent with the hypothesis that there is spontaneous ionization from the triplet level of the complex. Similar ionization of the triphenylene–pyromellitic dianhydride complex in various solvents has been observed by Pilette and Weiss[57]. They were able to deduce that the product predominates as ion pairs in dichloromethane, tetrahydrofuran and acetone, whereas in acetonitrile separated ions are favoured.

Achiba and Kimura[129] have been able to observe a triplet–triplet absorption of the 1-methylnaphthalene–pyromellitic dianhydride complex together with the formation of the acceptor anion in the transient absorption spectra following appropriate laser-flash excitation. Development of this ion is in two stages: a certain concentration, which is independent of introduced triplet quenchers, appears immediately after the laser pulse; thereafter there is a slower increase in concentration which is sensitive to oxygen. The rate constant of this further development is equal to the rate constant for the triplet–triplet absorption band decay. Achiba and Kimura[129] have concluded that ionic dissociation occurs by both excited triplet and excited singlet states for this system. The short-lived transients initially observed in the flash photolysis of pyromellitic dianhydride complex in the solvents ether, dioxan or tetrahydrofuran are attributable to the triplet state of the acceptor, but a long-lived species is also detected: this is the acceptor radical anion formed via the triplet. In acetonitrile solution the radical is formed mainly through the excited singlet state[130].

The photodissociation of perylene–pyromellitic dianhydride EDA complex into the radical ions $D^{+\cdot}$ and $A^{-\cdot}$, and the production of these ions by excitation of the perylene followed by electron transfer, has been reported by Hentzschel and Watkins[131]. Another complex which has been studied for its photodissociation is ethylbenzene–pyromellitic dianhydride[132].

Probably the most studied photochemical reaction involving an anhydride in which an EDA complex is postulated in the mechanism is the formation of a 2 : 1 adduct (4) from maleic anhydride and benzene[133–138]. Bryce-Smith and his coworkers propose the following scheme for the unsensitized reaction:

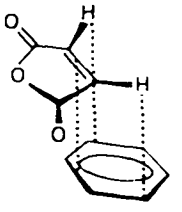


(3)

(4)

SCHEME 1.

Solutions of maleic anhydride in benzene show[139] enhanced absorption particularly in the region 270–290 nm which almost certainly contains intermolecular transition(s) of the EDA complex. Irradiation within this band, but at lower energies than those corresponding to the absorptions of either benzene or maleic anhydride alone, will promote the photochemical reaction. When the mixture is diluted with cyclohexane to the extent that only 3% of the reactants are complexed, compared with 30% in the absence of cyclohexane, no product is formed. These observations give support to a mechanism which involves excitation of a stable EDA complex. The n.m.r. chemical shift of the protons of maleic anhydride are considerably upfield in benzene solution compared with the signal when a carbon tetrachloride solution is used[140]. This provides supporting evidence, though of a more circumstantial nature, that an EDA complex is formed initially. The direction of the change of shift suggests that the electron donor–acceptor pair are in an *exo*-orientation (5) in the ground state. Kobagashi, Iwata and Nagakura[141]



(5)

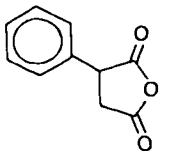
have given theoretical arguments for the ground and first-excited singlet states of the complex to have the double bond of the maleic anhydride centred over the benzene ring, the two molecules lying parallel to one another. An EDA complex

with these features in its geometry would be consistent with its involvement in the mechanism depicted in Scheme 1.

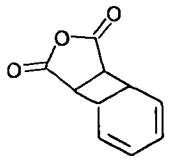
By comparison, the benzophenone-sensitized reaction, which has a very much higher yield[142], appears to proceed by energy transfer to maleic anhydride from the lowest triplet level of benzophenone, and has therefore a quite different mechanism[136,143].

Adducts similar to 4 have been obtained by the interaction of maleic anhydride with toluene, biphenyl and quinol[144]. Again the yields of product are considerably increased by the introduction of benzophenone as a photosensitizer. Under these conditions adducts are formed with other reactants including *t*-butylbenzene, chlorobenzene, *o*-xylene, *p*-xylene[144] and mesitylene[145].

Support for the involvement of the dipolar structure 3 in the unsensitized reaction of benzene with maleic anhydride has been obtained by carrying out the reaction in the presence of trifluoroacetic acid[146]. Formation of the product 4 was completely suppressed and phenylsuccinic anhydride (6) was formed. This product is to be expected from the protonation of 3.



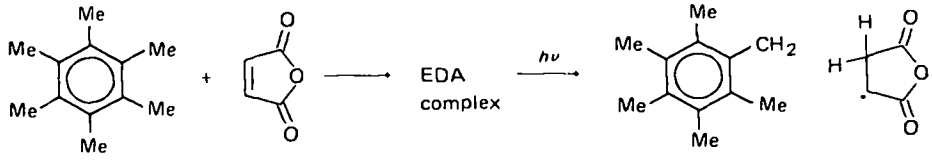
(6)



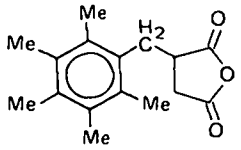
(7)

The earlier suggestion[133] that 4 is formed via the diene 7 is unlikely, since the reaction is insensitive to tetracyanoethylene which would be expected to trap 7[147].

Hexamethylbenzene and maleic anhydride react photochemically to form the substituted succinic anhydride 9. Raciszewski[148] suggested that in the excited EDA complex proton transfer occurred to form the radical pair 8 which then combined to form the product.



(8)



(9)

An EDA complex is a possible intermediate in the photochemical Diels–Alder reaction between maleic anhydride and anthracene[149]. Nagakura and his co-workers[141] have proposed configurations for the ground and first-excited singlet

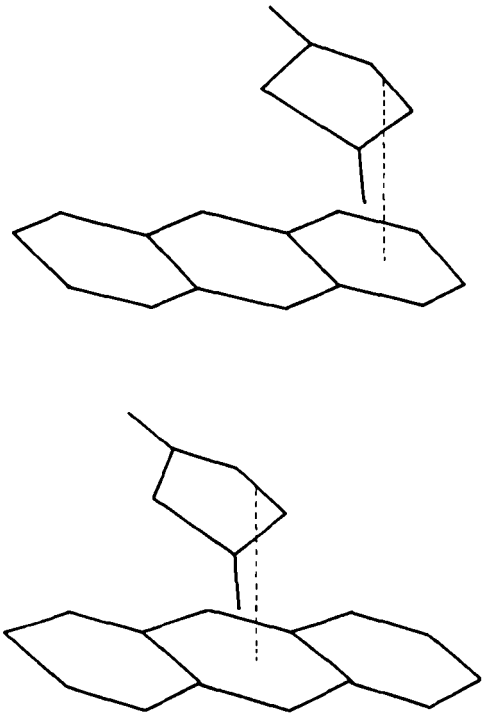
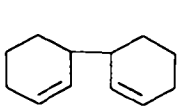


FIGURE 16. Calculated configurations of (a) the ground and (b) the first-excited singlet state of anthracene–maleic anhydride. Adapted from T. Kobagashi, S. Iwata and S. Nagakura, *Bull. Chem. Soc. Japan*, **43**, 713 (1970).

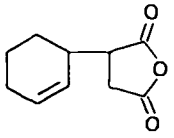
states of this complex as in Figure 16. The Diels–Alder adduct, formed by addition across the 9,10-positions of anthracene, is consistent with the reaction proceeding through the excited EDA complex. However, the thermal Diels–Alder reaction of anthracene with maleic anhydride also yields the 9,10-adduct. If the ground-state EDA complex with the configuration described in Figure 16(a) is on the reaction path, then it would have to be at an early stage in the reaction. This would not be unreasonable since the degree of charge transfer in the ground state, as opposed to the excited state, is known to be small. It should be pointed out that not all workers propose such a mechanism for the photochemical reaction. Thus Simons[150] prefers a mechanism involving the reaction of excited singlet anthracene with maleic anhydride. Certainly, in the dioxan solutions he used, the concentration of EDA complex is very small. It was argued that the fluorescence quenching of the anthracene by maleic anhydride indicated the fast removal of the excited singlet anthracene before an inter-system crossing to the triplet state could occur. However, Turro[151] has pointed out that this does not prove that the reaction proceeds by singlet anthracene since the EDA complex may be responsible for the quenching.

Irradiation of maleic anhydride in cyclohexene at wavelengths greater than 285 nm allows more than 98% of the radiation to be absorbed by the EDA complex (λ_{max} = 270 nm) as opposed to the free components. The products include

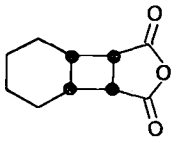
bicyclohex-2-enyl (**10**), cyclohex-2-enyl succinic anhydride (**11**) and the three tricyclic anhydrides, **12**–**14**, probably having the stereochemistry indicated[152].



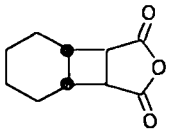
(10)



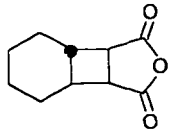
(11)



(12)

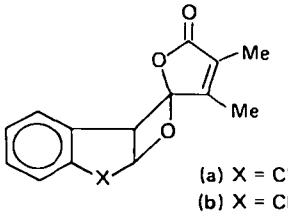


(13)



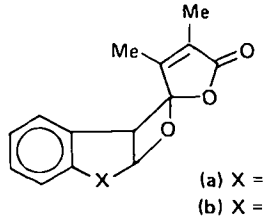
(14)

The formation of oxetans via EDA complexes of maleic anhydride and its derivations has been described by Farid and Shealer[153]. Thus the absorption spectra of benzene solutions of dimethylmaleic anhydride in the presence of indene indicate the formation of an EDA complex. Irradiation of the complex led to the formation of the oxetans **15a** and **16a**, along with **17** as well as traces of 1,1′-bi-indenyl. Likewise 1,1-dimethylindene and benzofuran form EDA complexes with dimethylmaleic anhydride to yield, on irradiation, the oxetans **15b**, **16b**, **15c** and **16c** along with **18a**, **19** and **18b** respectively. The phthalic anhydride complex



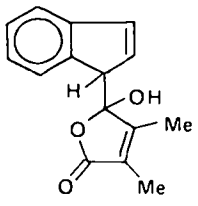
(a) X = CH_2
(b) X = CMe_2
(c) X = O

(15)



(a) X = CH_2
(b) X = CMe_2
(c) X = O

(16)



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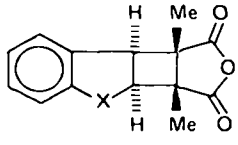
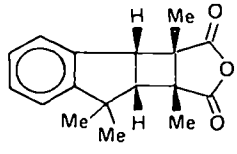
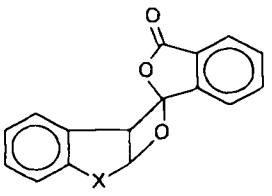


(18) (a) X = CMe_2
(b) X = O

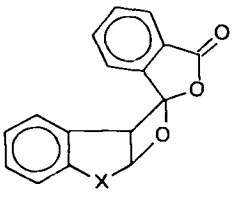


(19)

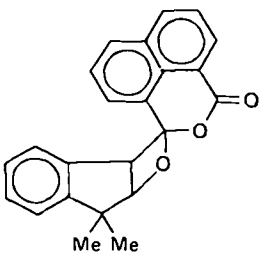
of dimethylindene when irradiated similarly yields the oxetans **20a** and **21a** whilst naphthalic 1,8-anhydride correspondingly gives **22**. The phthalic anhydride–indene complex yields a similar mixture of oxetans **20b** and **21b**. The ratio of **15** : **16** from



(20) (a) X = CMe_2
(b) X = CH_2



(21) (a) X = CMe_2
(b) X = CH_2



(22)

all three olefins is 4 : 1 or greater, the ratio of the corresponding products from phthalic anhydride, **20** : **21**, is about 1 : 1, and in the reaction of naphthalic 1,8-anhydride only the single, more sterically hindered isomer (**22**) is detected. The authors take this as implying that the overlap of the rings of donor and acceptor is favoured in the intermediate leading to the products.

The involvement of EDA complexes, including those of anhydrides, in polymerization reactions has been reviewed recently[154,155].

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER 6

Hydrogen bonding in carboxylic acids and derivatives

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I. GENERAL

A. Introduction

Hydrogen bonding (H-bonding) in carboxylic acids has been the subject of numerous studies, using a variety of experimental techniques as well as quantum-mechanical calculations, because here the H-bond phenomena are well pronounced and there are many types and degrees of bonding that can be relatively comfortably handled. Amides have also been thoroughly studied for all the above-mentioned reasons and also because of their importance as model compounds for peptides and proteins. Much less work has been done on other derivatives since, being at most only proton acceptors, they do not offer such a variety of H-bonded structures. These facts will also be reflected in the proportion of space devoted in this chapter to carboxylic acids and their respective derivatives. H-bonding of amino acids and other carboxylic acid derivatives of biological importance, as well as that of polyamides and polypeptides, is not included in this review. Although there are a good many books[1] and review articles[2] covering either H-bonding in general, or specializing in particular aspects thereof, a short summary should be useful at least to classify some of the concepts and terms to be used in the following sections and to indicate references pertaining to the most general methods of investigation.

B. Structural Aspects of H-Bonding

H-bonding is one of the most important specific interactions determining the arrangement of molecules and dynamic processes in solids and liquids. The basic types of association are shown in Figure 1. One of the principal means of characterizing H-bonds is by considering structural parameters (Figure 2), obtained mostly by X-ray and neutron diffractions[1d], or, for the gas phase, by electron diffractions. Microwave spectroscopy is of limited value because it can only be applied to molecules of limited size and having permanent dipole moments. The majority of the diffraction data, particularly the older ones, refer only to the distance between the heavy atoms, R, and this is also used in classifying the H-bonds.

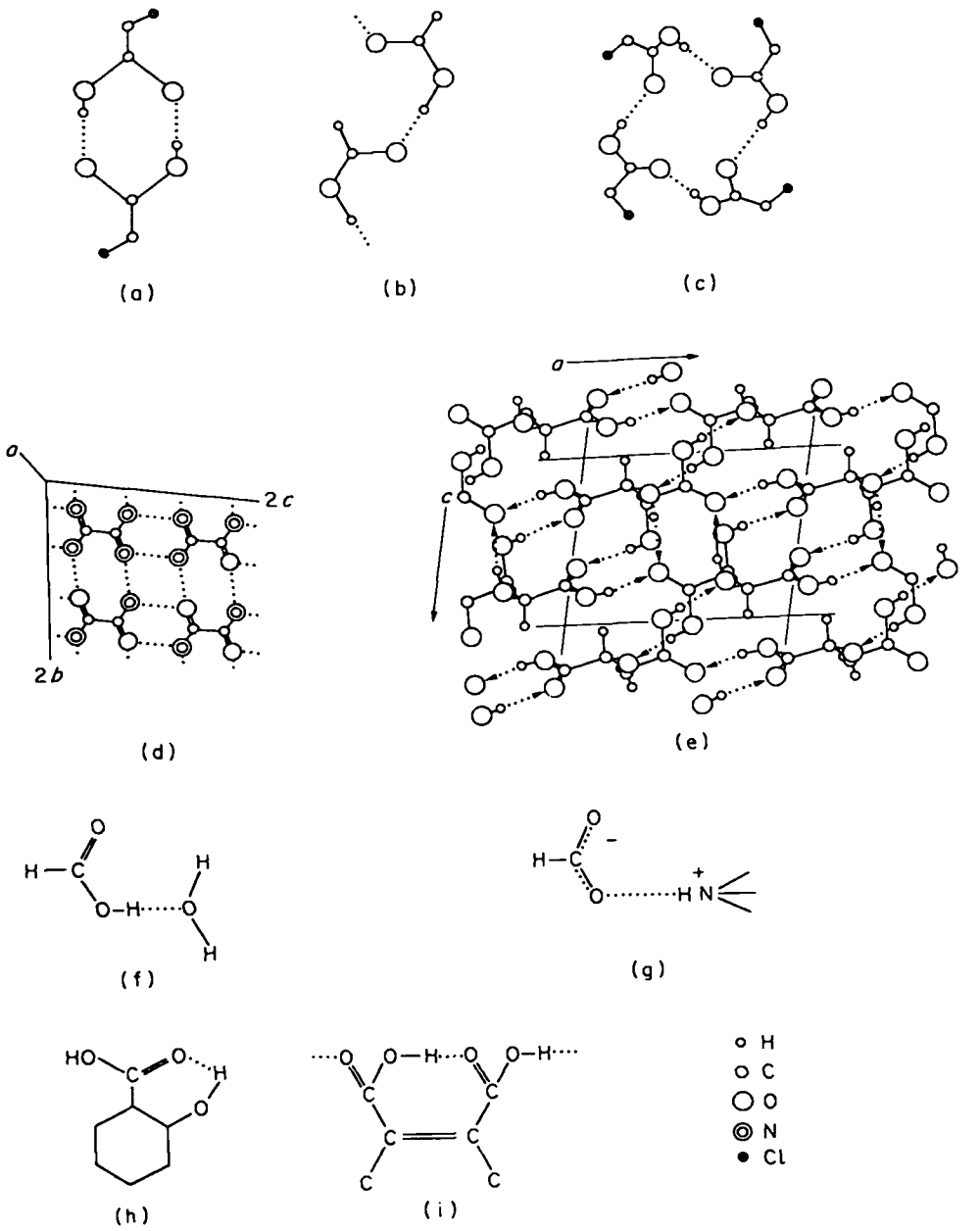


FIGURE 1. Examples of association structures by H-bonding. (a) Dimer (β-chloroacetic acid), (b) chain (formic acid), (c) tetramer (α-chloroacetic acid), (d) two-dimensional network (oxamide), (e) three-dimensional network (tartaric acid), (f) heteroassociation (neutral formic acid–water complex), (g) heteroassociation with proton transfer (formic acid–amine), (h) intramolecular H-bond (salicylic acid) and (i) intramolecular and intermolecular H-bonding (maleic acid).

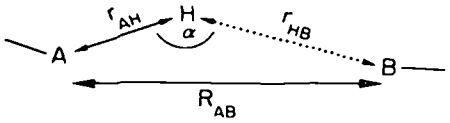


FIGURE 2. Molecular parameters characterizing H-bonds.

For instance, the OHO-type H-bonds* are usually considered to be long (weak) if $R > 2.8$ Å, intermediate if $2.6 > R < 2.8$ Å and short (strong) if $R < 2.6$ Å. However, a more complete characterization implies the position of the proton, i.e. the knowledge of r_{AH} and r_{HB} as well as of the angle α. One criterion for the existence of H-bonding is that R is shorter than the corresponding sum of van der Waals' radii, which is for the OHO atoms $R_{AB} \sim 3.4$ Å. The shortest observed OHO bonds are ~2.40 Å. The bonds connecting A and B, respectively, to the rest of the molecules also change by H-bonding.

The problem of the exact location of the proton becomes particularly intricate in the case of very short H-bonds, when one has to decide between the alternatives of having the proton in the middle and vibrating in a single minimum potential well (see Section I.F.2) or tunnelling between two minima. The answer cannot be obtained directly even from neutron diffractions[3].

C. Spectroscopy of H-Bonding

1. *Infrared Spectroscopy*

Infrared spectroscopy[4] is one of the most frequently used methods for investigating H-bonding. The changes in the infrared spectra caused by H-bonding reflect the changes of force constants, charge redistribution and the dynamic interactions. The main vibrational modes concerned are:

A—H . . . B stretching, ν (ν_a in symmetric bonds A—H . . . A)
A↓—H↑ . . . B↓ in-plane bending, δ
A^+—H^- . . . B^+ out-of-plane bending, γ
$\overleftarrow{A}$—H . . . $\overrightarrow{B}$ H-bond stretching, σ (ν_s in symmetric bonds A . . . H . . . A)

The stretching vibration (ν) of the A—H bond shifts from about 3650 cm^{-1} to 600 cm^{-1} in some symmetrical OHO bonds. $\Delta\nu$ is thus a useful characteristic of H-bonding. The band broadens, increases in intensity, and develops subsidiary maxima (see Section I.F.2).

Both deformation modes shift in the opposite direction. The higher frequency mode, usually called in-plane deformation (δ), is most often coupled to other vibrational modes and is therefore less useful for characterizing H-bonding, whereas the out-of-plane deformation (γ) is more characteristic and the shift attains up to 700 cm^{-1}.

Amongst the intermolecular modes generated from the rotations of the free molecules the so-called H-bond stretching (σ) is particularly important. It appears below 400 cm^{-1}.

Changes in frequency, intensity and band-width also occur with bands due to the

*In the following we shall refer only to this type of bond except if explicitly stated otherwise.

vibrations in which the bonds next to the H-bond forming atoms are engaged, e.g. of the proton-accepting group such as the carbonyl.

2. *Raman spectroscopy*

Raman spectroscopy has so far been less used in investigating H-bonding, partly because of the inherently weak scattering propensity of the modes involved, and partly because of the technical limitations. The latter has been recently overcome by laser excitation. The particular value of Raman spectroscopy is in the difference between the mechanism ruling the infrared absorption intensity and the Raman scattering power which is useful when looking for the operation of selection rules and hence in determining the symmetry of the H-bonded system.

3. *Nuclear magnetic resonance*

Nuclear magnetic resonance and relaxation methods offer several avenues of approach to problems of H-bonding in solids and liquids and, to a smaller extent, in the gaseous state. The magnetic properties of ^{1}H are exploited mostly, but ^{2}H, ^{13}C, ^{17}O, ^{15}N, ^{19}F and some other nuclei are also used. In solids, the dipolar shape of the signal is used to explore the geometrical arrangement of the signal proton in simple cases and the relaxation phenomena yield information about the proton dynamics[5]. The deuterium quadrupole coupling tensor, which may be determined from quadrupole splittings of the nuclear magnetic levels in crystals, is very sensitive to the charge distribution around the nucleus and hence to H-bonding effects. Other quadrupole nuclei like ^{14}N, ^{17}O and ^{35}Cl are also sensitive probes, both for the charge distribution and the dynamics. The tensor of the shielding which may be obtained from the more recently developed techniques for measuring the chemical shifts in solids[6] also yields very valuable information on the electronic charge surrounding the H-bonded proton and the more remote nuclei of ^{13}C and ^{17}O.

Most of the n.m.r. work concerns the chemical shifts in liquids. The proton resonance shows a low field displacement by H-bonding, roughly in proportion to the strength of bonding. Because of the rapid exchange the observed shift depends on the equilibrium constant and the chemical shifts of the free and bonded species, respectively. This is used for determining the thermodynamic quantities of H-bond formation in the liquid and gas phases[7].

The measurement of the correlation times gives information about the intra- and intermolecular motions and life-times of H-bonded aggregates. Besides the ^{1}H relaxation, $^{2}H_2$ and ^{17}O are also used in such experiments. However, due to the intricacies of the experiments and the difficult theoretical evaluations of the direct data there are relatively few results available.

Electron paramagnetic resonance spectroscopy (e.p.r.) is a valuable source of information on H-bonding in free radicals. For instance, the hyperfine contact interactions of the unpaired electron with proton yield information on the probability distribution of the former in the H-bond and hence on the nature of bonding. Proton tunnelling effects have also been observed[8].

4. *Electron spectroscopy*[9]

In the classic approach, i.e. absorption spectra, the effect of H-bonding on the proton-accepting moiety is most often observed because the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi$

transitions fall in the normal u.v. region. The effect usually consists of a blue-shift and change in intensity. On the contrary, the absorption of the proton donor shifts to the red. The shifts are thus in the same direction as for the change of the medium from less to more polar. The most interesting data are concerned with the proton-donating and -accepting propensities in the electronic excited states, which are often well above those in the ground state. The potentialities of photoelectron spectroscopy have not yet been exploited fully, although the published results are encouraging[10].

D. Thermodynamics and Kinetics[11]

The equilibrium $AH + B \rightleftharpoons AH \ldots B$ is characterized by the usual thermodynamic quantites ΔG^0, ΔH^0 and ΔS^0 which may be determined by a variety of methods. Most of the thermodynamic data have been obtained by the above-mentioned spectroscopic methods, but the direct calorimetric as well as the vapour-pressure and distribution methods are also much in use and the first is considered to be the most reliable. The lower limit of the enthalpies of formation ($\sim$ 1 kcal/mol) overlaps with the non-specific solvent effects whereas the highest observed enthalpy ($\sim$ 42 kcal/mol) is that of the $(FHF)^-$ ion[12]. The enthalpies of the strongest OHO systems are somewhat smaller[13]. Most of the data refer to equilibria in solution, which include the differences between the solvation energies of the free and bonded state; this eventually yields smaller values for the enthalpy compared to the gas phase, i.e. decreasing with increasing polarity of the solvent. In most H-bonded systems the entropy is linearly related to the enthalpy.

The formation and dissociation of H-bonds, which are very fast reactions, have been studied by relaxation methods[14], of which the temperature-jump and the ultrasound velocity measurements are the most appropriate. The association rate constants, which are of the order of 10^9 mol^{-1} s^{-1} at room temperature, and the enthalpies of activation suggest that the diffusion processes determine the rate of association.

E. Correlations

Since the frequency shift $\Delta\nu$ is a readily obtained characteristic quantity, relationships involving this are practically the most important. In solving structural problems the correlation between $\Delta\nu$ and R[15] is often used and it is also of importance for the dynamic theories. The long-ago proposed $\Delta\nu - \Delta H^0$ relation[16] has been much discussed, and its scope is now well established[17] and gives some clues as to various contributions to the H-bonding energy[18]. The relations between $\Delta\nu$ and the chemical shift and the acid–base properties of the donor and acceptor, respectively, are quite useful from the chemical point of view[19], but are restricted to very similar types of compounds.

F. Theory of the H-Bond

1. Electronic theory[2d,e,20]

In the early electronic theories of H-bonding the real systems were simulated by the three essential atoms and two pairs of electrons, and the changes in the main contribution to bonding energy were described as functions of interatomic distances using empirical parameters. Such simple model calculations have already shown that on reducing the distance between the heavy atoms the covalent

character of H-bonding increases, whereas at large distances only the Coulomb interaction is important. The modern quantum-chemical theories and the pertaining computational techniques within the framework of the molecular orbital (MO) theory allow all-electronic treatments of the complex considered as the 'supermolecule'. Hence the effects of H-bonding can be followed in all details. Various perturbation methods have also been applied, but their scope is more limited and therefore we shall very briefly review the main achievements of the supermolecule treatment. The theory in any of its numerous approximations, ranging from the popular semiempirical schemes up to the *ab initio* methods using large basis sets and including sometimes a part of the electron correlation energy, has been tested on simple systems like H_2O and HF dimers and polymers, pure and mixed, NH_3 and CH_2O complexes etc. On the other hand, large systems such as guanine and cytosine pairs have been treated at a rather high computational level[21].

The solution of the Schrödinger equation for different geometrical arrangements of the complex-forming molecules allows the predictions of the minimum energy configuration of the complexes. This is particularly important in cases where the formation of open and cyclic dimers and/or polymers is possible as in water, alcohols and amides, and the experiments do not yield unequivocal information on their relative proportions. The calculation of minimum energy distances and angles yields very good results when compared to available experimental data, provided that adequate computational procedures are used. However, the defects of the simpler methods are now sufficiently well known and can be compensated for; therefore they can be applied to large molecular systems for which the more sophisticated methods are uneconomical.

By computing the energy as a function of the proton coordinates potential surfaces for the proton motions are obtained. These surfaces, particularly the potential function for the proton stretching, are determining the dynamics of the H-bond and we shall return to this point later. One of the most interesting questions to be answered by the theory concerns the origin of the energy stabilizing the H-bond. Several computational schemes have been developed for the dissection of the energy difference ΔE_H between the free and H-bonded molecules into contributions from (classic) Coulombic energy, exchange repulsion, polarization, charge-transfer and dispersion. Although the results depend on the method and even the basis set used, all approaches agree in that the contributions qualifying the covalent character of the H-bond, in particular the charge-transfer, increase with decreasing R although the electrostatic contribution is dominant even in very strong bonds[22]. In fact, the localization of the molecular orbitals[23] shows the formation of an orbital between H and B which also appears in the experimental differential electron density maps obtained from X-ray and neutron diffractions[24]. Other characteristic changes such those as concerning the force constants, dipole moments, infrared intensities, magnetic shielding tensors and quadrupole coupling tensors can be obtained from the MO wave functions with success clearly depending on the quality of the wave function.

Starting with interatomic potentials calculated by quantum-chemical methods the statistical mechanical and molecular dynamical approaches yield rather precise descriptions of the structure of pure liquids and solutions[25].

2. *Dynamics of H-bonded systems*

Since the H-bond is weak compared to normal chemical bonds its responses to external mechanical, and particularly electromagnetic, forces, give rise to a number of peculiar phenomena such as proton conductivity and ferroelectricity. From the

chemical point of view, H-bonding is of great importance in proton transfer-processes between acids and bases.

Sensitive probes of H-bond dynamics are the vibrational spectra. The broadening and fine structure of the ν_{OH} and other bands are intimately connected with the H-bond dynamics. Attempts to explain the broadening by considering the proton dynamics alone have failed and the recent theories are based on the anharmonic coupling of the fast motion (ν_{AH}) with the slow one (σ_{AHB}). This interaction also explains the geometric mass effect and the trend of the ν_{OH}/ν_{OD} ratio which decreases from the normal value of $\sim\sqrt{2}$ in weak H-bonds to ~ 1 in strong, asymmetric ones[26]. The reader interested in the details and earlier hypotheses concerning the band-broadening and its structure should consult references 27 and 28. Here we shall only present the present state of theoretical work along the most relevant experimental facts. The theories proposed in the last few years are: (*i*) the Witkowski–Maréchal theory, (*ii*) the Bratos theory and (*iii*) the strong coupling theory. They have, in fact, much in common, but differ in the emphasis on some details and in the formalism. The first theory[29,30] is purely quantum mechanical and considers the isolated H-bonded system. The exciton type of coupling can be introduced for the case of dimers and crystals[31]. The essence of the theory is the frequency dependence of the ν_{AH} mode on the distance R as expressed by the parameter b:

$$b = h\left(\frac{d\omega_{AH}}{dR}\right)_{R=0} \approx (\omega_{AH}/2K_{aa})K_{aab},$$

where K_{aa} is the force constant of the AH bond and K_{aab} is the anharmonic coupling constant of the low frequency motion ω_{AH}. This theory accounts for the geometric and vibrational mass effects and permits a quantitative reconstruction of the spectrum. The band structure is due solely to transitions which are the vibrational equivalents of the Frank–Condon transitions in the electronic spectra. The theory may be extended to include the Fermi resonance between the ν_{AH} mode and combinations of internal modes considered earlier[32]. This raises the question as to whether this effect of the anharmonicity in the potential energy functions or the coupling with the low-frequency H-bond vibrations are the more important for the actual shape of the bond. In Bratos' theory[33], which is based on general postulates of non-equilibrium statistical mechanics, the Fermi resonance coupling mechanism is generally present and accounts for the structure in terms of combination bands separated by the so-called Evans holes[34]. In this theory the internal vibrations are treated by quantum mechanics whereas the external ones are described by the stochastic type of function. This approach is suitable for accounting for the influence of the molecular interaction in liquids and lends itself also to quantitative practical calculations. The strong coupling theory[28] is directed primarily towards H-bonded solids using methods of solid-state physics, but is also general.

Both the empirical[35] and *ab initio* calculated potentials predict, for small R_{O-O}, the double minimum situation, which may be symmetrical or not. Symmetrical double minima are expected only in homoconjugated ions $(AHA)^-$ and $(BHB)^+$ and, with decreasing R a single central minimum will result. The potential is very sensitive to the effects of electric fields originating in neighbour ions and H-bonds and has the tendency to become asymmetrical[36].

In the double-minimum potentials with low barriers proton tunnelling is possible, which may deeply influence the vibrational spectra and dynamical processes

involving proton motions such as the proton transfer between acids and bases[37], proton conductivity and ferroelectricity. The double-minimum potentials in biological substrates are a subject of growing interest[38].

Of particular significance for the dynamics are the cooperative effects which may arise in one and more dimensional H-bonded systems. Quantum-chemical calculations of potential energy in closed dimers (Section II.C) and polymeric chains[39,40] show that the barriers for coupled proton jumps are considerably lower than for single ones.

II. H-BONDING IN CARBOXYLIC ACIDS

A. Structural Aspects

1. Self-association

a. Neutral acids. The typical form of self-association of carboxylic acids is the closed centrosymmetric dimer. This association form is normally found with crystallized fatty acids from propionic on, in dicarboxylic acids from malonic on, and in simple aromatic acids as well as in many, more complex carboxylic acids. As exceptions appear the lower members of the former two series and some unsaturated *cis* dicarboxylic acids. We shall consider trichloroacetic acid, of which a very good neutron diffraction study has been made[41], as an example of dimer geometry (Figure 3). This will be followed by a short review of the above-mentioned exceptions, whereas the H-bonding of carboxylic acids with hetero association will be considered in Section II.A.2.

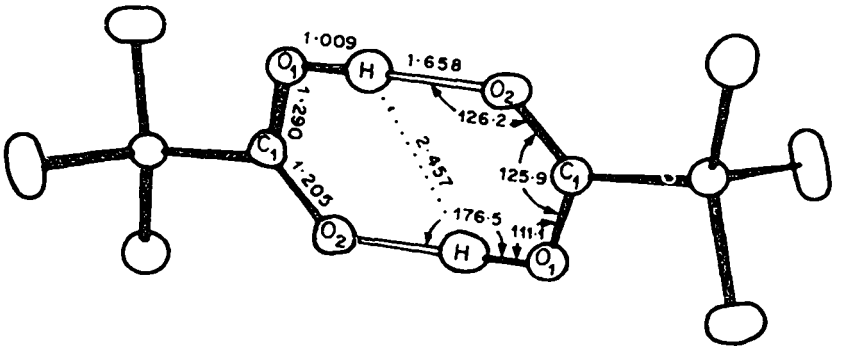


FIGURE 3. Molecular parameters of trichloroacetic acid dimer. After Jönsson and Hamilton[41].

The atoms forming the H-bonded dimer of trichloroacetic acid are close to planar and the hydrogen bonds are nearly linear. The two C—O bonds in this and some other dimeric carboxylic acids have significantly different lengths which are related to the proton positions. In many cases the distances are nearly equal (Section II.C). The distance between the oxygens, R, is in this example on the longer side of that typical for carboxylic acid dimers in solids. The majority of the results are between 2.63 and 2.65 Å. However, many of the data stem from the period in which the significance of the second decimal was rather dubious. In many crystals as well as in the gas phase and in dilute solutions the dimers are centrosymmetric. This is also apparent from the comparison of infrared and Raman spectra[42,43]. In some dicarboxylic and haloacetic acids the X-ray diffractions

suggest that the OHO angle differs considerably from 180°, the protons being either inward or outward of the dimeric ring[44].

By comparison of molecular parameters of dimers and monomers which have become available more recently from electron diffraction work, changes in the molecular framework induced by H-bonding can be systematized (for a compilation of data see Reference 45). The C—O bond lengths become more similar the C—OH bond being more affected and the O—H lengthening. The C—C—OH and C—C=O angles also become more similar. Deformations of the carboxyl group by H-bonding were also studied in the transition of fumaric acid from the gas phase to the solid[45]. Closed dimers of formic[46], acetic[47] and propionic[48] acids in the gas phase were investigated by electron diffractions. In all cases R seems to be larger than in the solids, i.e. near 2.7 Å. The increase in R by deuterium substitution[46] is of importance for the dynamic theory of H-bonding, yielding the anharmonic coupling parameter independently of spectroscopic data[30]. A number of mixed dimers involving fluoroacetic acid were observed in the gas phase by low-resolution microwave spectroscopy[49].

Formic acid forms in the solid H-bonded chains[50]. Two crystal modifications have been identified by infrared spectra. The molecular arrangement in each differs because of *cis–trans* isomerism[51]. Acetic acids also form chains and the structure has been investigated both by X-ray[52] and neutron diffractions[53]. Higher members of the fatty acid series crystallize as dimers. Oxalic acid appears in two crystal forms, α and β[54]. The molecules in the β-form are associated by single H-bonds into infinite chains, whereas the chains in the α-form consist of dimerized units as in most other mono- and dicarboxylic acid crystals. The H-bonds in the dimeric form are shorter than in the chains in contrast to the case of formic acid. The differences in R values are probably due to crystal packing effects. Monomeric oxalic acid forms in the gas phase weak intramolecular H-bonds[55].

α-Monochloroacetic acid is present in the solid in tetrameric rings, whereas the β-form contains dimers[56,57]. Maleic[58] and furanedicarboxylic[59] acids contain one, rather short, intramolecular H-bond besides the intermolecular ones joining the molecules into chains. The H-bonding in maleic and some related acids has been investigated and discussed by James and Williams[58].

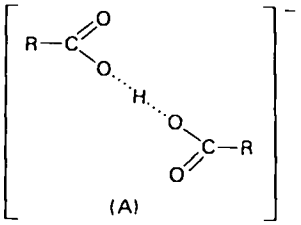
The problem of the structure of liquid carboxylic acids, particularly of the lower fatty acids, is one of long standing and still hot. It is generally accepted that in dilute solution in non-polar solvents the equilibrium between monomers and closed dimers is the dominant one. However, in pure liquids and concentrated solutions definite experimental evidence for the departure from simple, regular dimers has been given at least for the lower fatty acids. Probably the oldest suggestions for the existence of open dimers or chain structures stem from the dielectric polarization measurements. Centrosymmetric dimers should be non-polar but dipole moments of 0.862 D have been found with various acids. The dipole moment has been interpreted as due either to atomic polarization[60] or dimer distortion[61]. The ^1H chemical shift, which usually increases with dilution, shows a minimum just above 0.1 M in the case of acetic and trifluoroacetic acids in CCl_4. This has been interpreted in terms of weaker H-bonding in oligomeric associates which should be present at higher concentrations[62,63]. The presence of a second $\nu_{C=O}$ band in the infrared spectrum of acetic acid has been ascribed to the existence of open dimers and oligomers[64]. Significant differences in the infrared spectra of formic acid on dilution with CCl_4 have also been ascribed[65] to a gradual transition from polymeric to dimeric species, since the spectrum of the pure liquid is similar to that of the solid acid. A more concrete model of the liquid has been proposed by Tomlinson

and coworkers[66]. Bellamy, Lake and Pace[67] have suggested that the breadth and shape of the ν_{OH} band of acetic and some other acids may be due to an equilibrium between open chains and cyclic dimers. Dielectric relaxation spectra of pure acetic acid and solutions above 0.07 M in benzene are also not consistent with the presence of non-polar dimers only but rather indicate linear or cyclic polar oligomers[68]. The three lowest members of the series have been investigated by low-angle X-ray scattering which suggests the presence of molecules connected by two H-bonds and chains, the former being dominant and increasing in proportion from formic to propionic acid[69]. In an earlier study using the same technique a chain structure of liquid formic acid was proposed[70]. The transition between cyclic and open dimers seems to be involved in the phase changes of liquid crystalline *p*-heptoxybenzoic and *p*-octoxybenzoic acids. A direct relationship between the phases and the type and extent of H-bonding in these acids has been found by observing the temperature dependence of the ν_{OH} and $\nu_{C=O}$ bands[71].

The most thorough study of the structure of pure liquid and CCl_4-diluted acetic acid has been made by Berg and coworkers[72]. They have measured the proton magnetic relaxation rates of the methyl and hydroxyl groups. Considering the interatomic distances given by the low-angle X-ray scattering and using the statistical mechanical approach these authors have derived model atomic-pair distribution functions. The closed dimer appears at mole fraction $\chi \lesssim 0.3$ in a strongly folded form which has, however, to be considered as a dynamical average. In the pure acid, a third molecule joins it so that the polar groups are central and the methyl groups peripheral. Corresponding studies have also been made for propionic and butyric acids[73] and for formic acid[74].

b. Homoconjugate ions. Ions of the general formula $(AHA)^-$ appear as a stage in the neutralization of acids which may be observed in potentiometric titrations, by electrical conductivity and by vapour pressure measurements. Several papers deal with these aspects[75,76] including the determination of stability constants[77,78]. Other proton–acid ratios are also possible.

Many salts containing homoconjugate ions exist in the solid phase and their structures have been elucidated by X-ray and neutron diffractions[79,80]. The salts containing the acid and the conjugate base in a 1 : 1 ratio are of particular interest because the H-bonds are stronger here than in the neutral acid dimers or multimers. From the structural point of view the acid salts were classified by Speakman[79] as type A and B. In type A the two acid moieties are related by symmetry, e.g. KH trifluoracetate[81], whereas in type B they are not, e.g. KH acetate[82]. In the latter the bond lengths of the acid molecules approach more or less those of the neutral



and ionized acids, respectively. Thus in type A acid salts the H-bond, having $R = 2.44(6)$ Å on the average[79], may in fact be symmetrical, whereas in type B, where R tends to be slightly longer, the H-bond is asymmetric. In the pseudo-A type the two halves are not related by symmetry, but are nevertheless of equal

dimensions and thus the H-bond might eventually be symmetric. Some structures in which the acid–conjugate base ratio is 2 : 1 are also known[83]. The R values are longer than in the 1 : 1 acid salts, the neutral and ionized species being clearly distinguishable. The dicarboxylic acids give rise to acid salts having chain structures in which the H-bonds may occupy C_2 (e.g. KH succinate[84]) or C_i sites (e.g. RbH glutarate[85]). These are candidates for symmetrical H-bonding, whereas in others, e.g. K and NaH oxalates[86], the H-bond is on a general position. Acid salts of maleic[87] and some substituted maleic acids[88,89] may form very short (~2.41 Å) intramolecular H-bonds, or intermolecular ones, depending on the cation and the state[89]. Possibly the shortest intramolecular H-bond was found[90] in the monorubidium salt of furanetetracarboxylic acid (2.39 Å). However, the proton has not been located, as in the case of maleates, where it is certainly centred on the O—O line[87,88]. In solution the intramolecular bond is dominant even in cases where intermolecular bonding exists in the solid, e.g. *o*-phthalates[91]. Deuterium substitution in the H-bond causes in some cases a phase change to lower symmetry (e.g. hydrazinium deuterium oxalate[92].

2. *Molecular complexes of carboxylic acids (including those containing N and O) with bases*

Although a large number of solid complexes of carboxylic acids with ionic (other than the conjugate) or neutral bases have been chemically identified[93] and investigated by spectroscopic methods[94], there are only a few structures which have been determined by X-ray diffraction. In this paragraph we shall only deal with examples for which the X-ray structural data are available. Others will be mentioned in Section II.B.1.b. The simplest base to which the carboxyl group may bond is water. In the hydrates of acetylenedicarboxylic acid[93] and oxalic acid the COH . . OH_2 bonds are rather short (R = 2.56 and 2.50 Å, respectively[95–98]). Both are notable as examples of the positive mass effect on R. Further examples of COH . . OH_2 bonding are orotic acid (vitamin B_{13})[99], pyromellitic[100], hemimellitic[101] and dihydroxyfumaric acid[102] dihydrates. The bonding in acid hydrates is discussed by Takusagawa and Shimada[101]. However, in the *p*-hydroxybenzoic acid monohydrate the dimeric structure is preserved and the phenolic hydrogen is bonded to the water oxygen[103]. The C(=O)OH . . H_2O bonds are in general shorter than the H-bonds in dimers and obviously energetically more favoured.

An extremely short H-bond of R = 2.40 Å was found in the pyridine–trichloroacetic acid complex[104] and a somewhat longer one (R = 2.496(3) Å) in the complex of this acid with triphenylphosphine oxide[105]. 2-Methylpyridine-*N*-oxide forms a complex with fumaric acid, the O . . . O distance being 2.517(6) Å[106]. A solid complex with a complicated H-bond network is formed between formic acid and formamide[107]. Trifluoroacetic acid–amide complexes in the form of closed dimers are also observed by low-resolution microwave spectroscopy[49].

Examples of intermolecular H-bonding of carboxylic acids containing acceptor groups other than the carboxylic C=O should be mentioned here. Such bonding appears with pyridinecarboxylic and aminobenzoic acids. In pyridinecarboxylic acids the usual dimer formation may be replaced by COOH . . N bonding as in nicotinic[108] and dinicotinic[109] acids. The OH . . . N bonds in the latter are very short (2.515 Å) and the OH . . . O bonds formed by the remaining carboxyl group are also rather short (2.594 Å). In other pyridine dicarboxylic acids ionization occurs. Thus, in the 3,4-isomer one group is ionized and accepts protons from the

non-ionized group of another molecule as well as from the NH^+ group. The OH . . . O bond is very short (2.514 Å), obviously because the COO^- group is a stronger acceptor than COOH[110]. In the 2,3-isomer one carboxyl group is also ionized and is the acceptor for the other carboxyl from the same molecule[111]. Thus a very short, but asymmetric, intramolecular bond is formed (2.398 Å). This acid has also been investigated by neutron diffraction and the structure is well reflected by a quantum-chemical calculation[112]. In the 2,6-dipicolinic acid monohydrate the carboxyl groups are each connected by one COH . . O=C bond of 2.561 Å length and one COH . . OH_2 bond. The nitrogen atom is obviously screened by the two neighbour carboxyl groups and does not enter into any H-bonding[113]. Similarly, in the *trans*-3-(6-methyl-2-pyridilthio)-propenic acid the nitrogen is not an acceptor and the carboxyl groups are bonded to centrosymmetric, closed dimers[114].

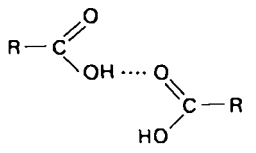
Anthranilic (*o*-aminobenzoic) acid appears in three crystal modifications, one of which has been investigated by X-ray diffraction and the others by infrared spectroscopy only[115]. The polymorphism has been investigated by DTA and DSC[116]. The modification I consists[117] of two types of molecules, one neutral and one zwitterionic. They are connected by short (2.543) O—H . . O and longer NH . . O bonds. Intramolecular N—H . . O bonds are also present. In the other two forms normal carboxylic dimers seem to be present[115]. This is also true of the 3′-trifluoromethyldiphenylamine-2-carboxylic acid[118], *p*-aminobenzoic acid[119], *p*-aminosalicylic acid[120] and 2-amino-3-methylbenzoic acid[121]. In 1-thiacyclobutane-3-carboxylic acid-1-oxide there is OH . . . OS bonding rather than dimer formation, although the bond is of comparable length as between carboxyl groups (2.63 Å)[122].

In hydroxycarboxylic acids such as tartaric[123], tartronic[124] and citric[125], dimer formation persists. However, in glycollic acid[126] the carboxyl group bonds to the α-hydroxyl of the neighbour molecule.

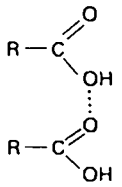
3. Carboxylic acid–water systems

The state of association of carboxylic acids, particularly of fatty acids, in moderately concentrated aqueous solution, is of considerable interest because these systems represent good models for the study of hydrophobic interactions[127]. The first approaches stem from the trends in activity and conductance on dilution in water as compared to the dimerization constants obtained from vapour pressure. The fact that the activity and conductance measurements for concentrated solutions were less than predicted by extrapolation of more dilute solutions were ascribed to dimerization[128,129]. However, Raman spectroscopic data[130] contradict this, indicating that there are few cyclic dimeric forms in a predominantly aqueous solution. That water will disrupt H-bonding to dimers might be expected by considering the crystal structures of hydrates of carboxylic acids (see Section II.A.2) and this is also evident from infrared spectra of carboxylic acids with added water[131]. Several other proton-accepting solvents are also known to disrupt the dimeric H-bonding (Section II.B.1.b). The apparent fitting of dimerization constants obtained from vapour pressure data to the activity–conductance anomaly is caused by the neglect of hydrated acid species in the vapour phase[132]. The question as to what sort of association is actually present in the carboxylic acid–water systems may be approached by considering the hydrophobic interaction between the hydrocarbon residues of carboxylic acids, and this would favour open

dimers of type **1a** over those of type **1b**. The importance of hydrophobic interactions is reflected by the fact that formic acid shows entirely different behaviour to acetic acid and also that the trends of higher aliphatic acids show increasing dimerization with the lengthening of the alkyl chain[133].



(1a)



(1b)

The application of n.m.r. relaxation time measurements coupled to statistical mechanical modelling of pair distribution functions[134] leads to a more definite representation of acetic and higher fatty acid–water systems. At low dilution, open dimers **1b** and closed dimers predominate with one or two acid molecules added sideways so that star-like clusters are formed. On dilution, the hydrocarbon ends tend to aggregate to form open dimers **1a** and higher associations. Folding of dimers occurs in a dynamic way. The equilibria and dynamics depend on the length of the hydrocarbon chain.

A particularly interesting problem of structure and H-bonding in water–acid–soap systems is that concerning liquid crystals. It has been studied by deuteron magnetic resonance spectroscopy[135].

B. Spectroscopy of H-Bonding in Carboxylic Acids and their Complexes

1. Vibrational spectra

a. Carboxylic acids. The pronounced broadening and submaxima on the ν_{OH} bands of H-bonded carboxylic acids have made them a very attractive subject for investigation. The theoretical aspects have been dealt with in Section I.F.2. A substantial part of the experimental investigations was aimed at clarifying the main factors influencing the shape of these bands, especially the role of the Fermi resonance. Isotopic substitutions for atoms other than the H-bonded protons are particularly relevant because such substitutions do not influence for all practical purposes the force constants. Studies were made mainly on isotopic acetic acids[64,136,137], and it was shown that some submaxima are indeed removed by isotopic substitution. However, the fundamental phenomena of broadening and, probably, the overall shape of the ν_{OH} band can only be explained by dynamical theories[28]. Several dimeric carboxylic acids have been recorded and the spectra compared with the theoretically calculated ones[138]. The calculated spectra of α- and β-oxalic acid are particularly impressive[139]. The location and H-bonding behaviour of some other bands, particularly the $\nu_{C=O}$ and the OH deformation bands, is also of importance with respect to the role of their combinations enhanced by Fermi resonance[140]. The normal coordinate calculations on monomeric and dimeric acids show the influence of H-bonding on the force constants pertaining to vibrations such as $\nu_{C=O}$, ν_{C-O} and γ_{OH}[141,142]. Calculations of the crystal force fields of benzoic[143] and succinic[144] acids have been made. For the testing of theories it is necessary to consider all the spectral details, including

precise intensity data, polarization characteristics as well as the temperature and mass effects. This induces new and more sophisticated experimental work such as the recent investigation of the ν_{OH} band in solid formic acid[145]. The determination of the transition probabilities of the H and D species of several carboxylic acids has revealed a very unusual isotopic effect of H-bonding, the isotopic ratio being close to 2 instead of $\sqrt{2}$ as for normal oscillators[146].

From the theoretical point of view the next most important vibrational mode is the low frequency one, σ_{OHO}. The relevant force constant may be related to

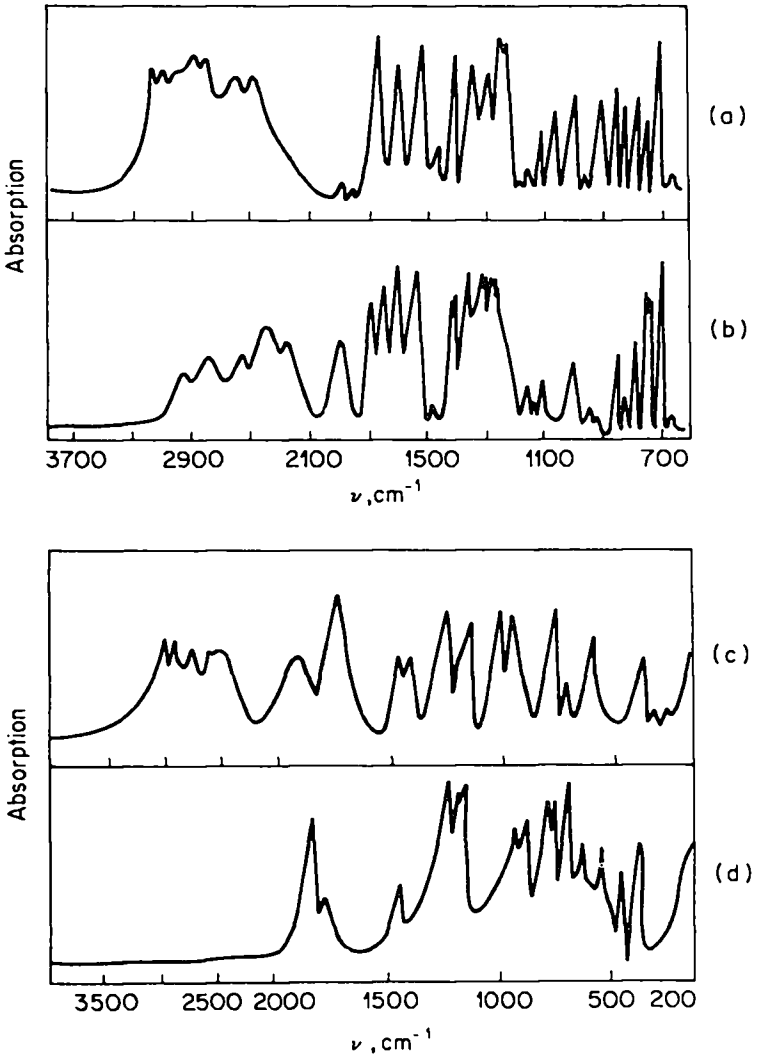


FIGURE 4. Examples of infrared ν_{OH} absorption patterns of H-bonded systems with increasing bond strength; (a) carboxylic dimer (*p*-nitrobenzoic acid), (b) acid salt of B type (KH-di-*p*-nitrobenzoate), (c) acid–base complex (dichloroacetic acid–dimethylsulphoxide) and (d) acid salt of A type (KH-bistrifluoroacetate).

the strength of the H-bonding. The band has been located in the spectra of several simple carboxylic acids and its frequency used in normal coordinate analyses[147,148].

b. Acid salts and molecular complexes. The increasing strength of H-bonding of the carboxylic OH group to the ionic carboxylate or phenolate, and to many neutral bases, particularly those containing an X=O group (X = N,S,P,Se,As), is reflected in the gradual shifting of the ν_{OH} band to lower frequencies (Figure 4). The general appearance of the spectra is not influenced by the base, i.e. similar spectra may be obtained either with complexes of carboxylic acids with oxo bases or acid salts[149]. When the centre of gravity of OH falls between 2700 and 2000 cm^{-1} a characteristic trio of bands appears, e.g. in KH phthalate[150] and in complexes of chloroacetic acids with sulphoxides[151,152]. Similar spectra were also obtained with carboxylic acids and pyridine bases[153]. The Fermi resonance has been made responsible for the appearance of this type of spectrum designated as (*i*) for classification purposes[149], but a hypothesis based on the strong coupling theory has also been put forward[28]. With still stronger bonding these bands are becoming weaker and the main ν_{OH} band moves in the region below 2000 cm^{-1}, e.g. in some acid oxalates[154]. When the ν_{OH} band is nearer to 1000 cm^{-1} and the H-bond is still asymmetric, overtones in the region above 2000 cm^{-1} become quite weak. The acid salts of type A and pseudo-A (Section II.A.1) have spectra of type (*ii*), with the characteristic absence of bands above 2000 cm^{-1} and the presence of a very strong adsorption between 1100 and 600 cm^{-1} [149]. Here the problem of the statistical (as reflected by the crystallographic symmetry) and the true (characterized by a single, central minimum in the potential energy function) symmetry becomes acute. In principle the problem should be resolvable by considering the operation of the selection rules. However, most of the systems of this type are rather complex and display many bands that are not relevant to the problem. Moreover, the crystal field splittings complicate the spectra. Absorption and reflection spectra of single crystals together with Raman spectra have been studied with the aim of establishing the operation of the selection rules[155,156]. Although the results favour symmetrical bonding in some examples[157], some details of the spectra remain to be clarified. It is interesting to note that type A and B acid salts can be readily distinguished by their spectra[158] and particularly by their different ν_{OH}/ν_{OD} ratios.

Spectra of type (*ii*) are also found in acid–base complexes, e.g. trichloroacetic acid–pyridine-*N*-oxide[151], and with some acid salts in the liquid state[159], provided that the cation is large such as tetrabutylammonium. In some *N*-oxide–carboxylic acid complexes the existence of $(AHA)^-$ along with $(BHB)^+$ homoconjugate ions has been claimed from the i.r. and n.m.r. spectra[160].

In acid salts with intramolecular H-bonding, e.g. KH maleate, the ν_s OHO band which is characteristic of the type (*ii*) spectra is very weak and may be detected only in single crystal spectra[161].

With sufficiently strong acid–base pairs proton transfer occurs, which is noted by the appearance of carboxylate bands in the infrared spectra. The ion pairs may still be very strongly bonded, e.g. trifluoroacetic acid–triphenylarsine oxide complex[162]. With appropriate acids and bases it is possible to obtain spectra similar to those in the neutral complexes[163]. However, the appearance of submaxima in the ionized complexes is determined by the OH^+ (or NH^+) entity. A very peculiar i.r. spectrum characterized by an extended strong continuous absorption results from aqueous solutions of acids, e.g. trifluoroacetic[164]. It is due to proton tunnelling in mutually polarizing H-bonds of the asymmetric double minimum type[165].

2. *Other spectroscopic investigations*

There is relatively little published electron spectroscopic work concerning H-bonding of carboxylic acids. The $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of the carbonyl group which should be most sensitive to H-bonding are rather far in the ultraviolet region (~58,000 and 68,000 cm^{-1} in acetic acid[166]). Blue-shifts were observed on dimerization and discussed by Barnes and Simpson[166]. Association effects on the $n \rightarrow \pi^*$ transition of gaseous trifluoroacetic acid were also observed, but the shift appears to be to the red. No comment is given to this[167]. The H-bonding sensitive bands of aromatic acids are not due to transitions localized in the carbonyl chromophore, but to excitations from orbitals including the aromatic system. Thus the H-bond effects on electronic energies may combine with steric configurational effects. The absorption near 290,000 cm^{-1} of benzoic and some substituted benzoic acids in hexane shows a red-shift with increasing concentration and has been used to determine the dimerization constant[168]. Polarized spectra of acetylsalicylic acid crystals (aspirin) have also been studied in detail[169]. Association effects have also been observed in 1- and 2-naphthoic acids in which the state of H-bonding also affects the coplanarity of the carboxyl groups and the aromatic ring. From the delayed excimer fluorescence of 1-naphthoic acid the formation of tetrameric excimers in the crystal was inferred[170].

Photoelectron spectra of the lower fatty acids, of trifluoroacetic acid and of mixed dimers have been recorded and analysed[10]. By assigning the bands to ionizations from particular molecular orbitals of monomers it was established that dimerization changes most of the ionization potentials up to 0.5 eV. The changes are consistent with the electronic theory of H-bonding, i.e. the ionization potential of an electron from a non-bonding orbital of the OH group is decreased whereas that of the C=O group is increased. It is interesting to note that the changes in ionization potentials of the mixed dimers indicate H-bonds of unequal strength again in agreement with theory.

From the point of view of the electronic theory the most interesting question in the u.v. region is that of charge-transfer (CT) bands which correspond to the electronic excitation from a non-bonding orbital of the proton acceptor to an antibonding orbital of the proton donor. Such a band has been observed by Nagakura in solid potassium hydrogen maleate[171] and recently this was substantiated by more detailed experiments and a CNDO/2 calculation augmented with some configurational interaction[172]. However the assignment of the 211 nm band to a charge-transfer transition has recently been challenged on the grounds of a CNDO/S CI calculation, the result of which prefers the assignment to a $\pi-\pi^*$ transition[172a]. Charge-transfer bands were recently observed in acetic acid–amine systems and their origin substantiated by MO calculations[174]. A previous claim for CT bands in carboxylic acid dimers was withdrawn[173].

Finally, it should be mentioned that carboxylic acids have often been used as proton donors in investigations of the change of basicity of various bases in the electronic excited states. The difference in H-bonding between the ground and excited electronic state shows up in the shift of fluorescence bands as well as in the luminescence yield and can be be used also for the determinations of equilibrium constants in the excited states provided that the life-times are sufficient to allow the establishment of an equilibrium[175].

Out of the numerous applications of n.m.r. spectroscopy to H-bonding one would inquire first about the chemical shift of the proton in carboxylic acid dimers. Although in general the shift is a useful characteristic of H-bonds, its determination in this particular case is difficult both because of the stability of the dimers even at

highest, yet measurable, dilutions or lowest vapour pressures, and of the influence of traces of water. The monomer resonance frequency can be obtained only by careful extrapolation of the concentration dependence of the shift. For acetic acid in the gas phase the difference between the monomer and dimer shifts is 523 ± 28 Hz (at 100 MHz) and in trifluoroacetic acid it is 561 ± 14 Hz[176]. Similar values have also been obtained for acetic and propionic acid in CCl_4 solution[63,177].

The chemical shift in liquids reflects only the isotropic part of the shielding tensor σ. The components of σ and the orientation of the axes gives far more precise characteristics of bonding, and they can be obtained by applying multiple pulse techniques to crystals. Using it on powders part of the information is lost but nevertheless the principal values of σ may be obtained. The shielding anisotropies of the carboxylic proton have been determined on a series of carboxylic acid powders by Haeberlen and Kohlschütter[178]. A precise study of the single malonic acid crystal has been made by Haeberlen and coworkers[179], of oxalic acid dihydrate by Ernst and coworkers[180] and of α-oxalic acid by Van Hecke and coworkers[181]. The proton shielding tensor is relatively strongly anisotropic $\Delta\delta$ ($= \delta_{\parallel} - \delta_{\perp}$) being of the order of 18 p.p.m. This figure may be compared with the isotropic proton chemical shifts which are within the range of 15 p.p.m. The $\Delta\delta$ varies with the strength of H-bonding. The shielding is nearly axially symmetric around the H-bond axis and the bond direction is the most shielded one. These facts are discussed in terms of various magnetic contributions in References 179 and 182. Relations between the chemical shift and acidity in the solid state are sought by Rozenberger[183].

A H-bond characteristic comparable to the shielding is the deuteron quadrupole coupling constant (DQCC)[184] which has been determined for a relatively large number of H-bonded systems, including some carboxylic acids. The DQCC of formic acid crystal[185] is 165 ± 2.7 kHz with the asymmetry parameter $\eta = 0.125 \pm 0.030$. The former value, compared to the DQCC of the monomeric formic acid by microwave spectroscopy which is 261 ± 3 kHz[186] is characteristic of H-bonds with R = 2.65 Å and similar DQCC have also been obtained with other dimeric acids[187,188]. Significant for the sensitivity of DQCC to H-bond strength is the difference between malonic[187] and 1,1-cyclobutanedicarboxylic acid[188] and also between the two different H-bonds in the latter ($\Delta \sim 7$ kHz). Corresponding to a shorter R, the DQCC in oxalic acid dihydrate[189] is 139 kHz. It is interesting to compare the anisotropy of the chemical shift tensor[179] and of the quadrupole coupling tensor in malonic acid[187]. Both the most shielded direction and the maximum electric field gradient are very nearly along the H-bond direction (8° and 4°, respectively).

Although the carboxyl carbon is only indirectly involved in H-bonding its shielding is quite considerably affected and this has been used in dilution studies of acetic acid with polar and apolar solvents[190]. The solvent effects span a range of 7 p.p.m. Increasing H-bonding on both the carbonyl oxygen and on the hydroxyl group result in a decreased shielding of the carboxyl carbon. The change in shielding on dilution in cyclohexane is very small (1 p.p.m.). The larger shifts in chloroform and acetone were used for estimating the dimerization constants. ^{13}C shifts of formic, dichloroacetic and trifluoroacetic acids in various carbonyl solvents are given in Reference 191. The ^{13}C H-bonding shifts in formic acid were also calculated by the INDO method[192].

High-resolution ^{13}C magnetic resonance in solids is a recent, very valuable addition to the n.m.r. techniques. Analogously, as in the case of high-resolution proton magnetic resonance in solids, it turns out that the shielding tensor anisotropy of ^{13}C is more sensitive to H-bonding than the isotropic shift. The difference

in the isotropic ^{13}C shifts of acetic and thioacetic acids (neat liquids) is only 16 p.p.m., whereas for the σ_{22} component the difference (in crystals) is 46 p.p.m.[193]. Most of this difference is due to the different strength of H-bonding in both acids. The other components show smaller differences.

An interesting result concerning the proton distributions in dimers of benzoic acid was obtained by Kempf and coworkers[194]. The x axis of the tensor of the carboxyl carbon shift is within 3° of the OCO angle bisector which indicates the equivalence of both C—O bonds. This is in agreement with the fact that both C—O lengths differ by only 0.05 Å[195], which is indicative of a disorder in proton positions.

The ^{17}O magnetic resonance is obviously attractive but measurements are difficult without isotopic enrichment. Hydrogen bonding when the hydroxyl group acts as donor causes a downfield shift which is larger than the shift in the same direction when accepting. The carbonyl oxygen displays an upfield shift. Knowing the individual contributions of both groups from breaking the dimer H-bond and the formation of new OH—solvent bonds it is possible to derive equilibrium constants for the formation of acetic acid–solvent complexes[196]. The dilution of acetic acid by water, acetone, acetonitrile and cyclopentane has been studied. The chemical shifts of both oxygens merge to approximately the average between the shift of the hydroxyl and carbonyl groups, respectively. The dilution shift in cyclopentane is, similarly to the ^{13}C shift, only ~1 p.p.m. relative to the pure acid, whereas in acetone and acetonitrile they are ~13 p.p.m. Correlations between ^{1}H, ^{13}C and ^{17}O shifts of acetic acid on dilution with cyclohexane were sought by Ziessow and coworkers[197].

N.m.r. methods have been applied to the problem of symmetry of H-bonding in acid salts. The DQCC and asymmetry parameters have been measured on KD trifluoroacetate[198], on KD maleate[199] and on triglycine sulphate[200]. All these H-bonds are extremely short (~2.4 Å), but the DQCC of the first two is very low (~55 kHz) whereas it is higher in the latter (~79 kHz). This corroborates other evidence that the H-bond is symmetrical in the former two whereas it is asymmetric in the latter[201]. ^{35}Cl quadrupole resonances have been measured for several acid salts of mono-, di- and trichloroacetic acid[202,203]. The equivalence or otherwise of the chlorine signals are used as evidence of the symmetry of the H-bond. Since the ^{35}Cl resonance is in the MHz region the conclusions are valid at this time-scale. However, the results are in agreement with the much shorter infrared time-scale[158].

^{35}Cl n.q.r. has also been applied to the study of structure and H-bonding in complexes of some amides and amines with trichloroacetic acid[204] and of pyridine with this and other chloroacetic acids[205].

C. Theoretical and Proton Dynamics

Quantum-chemical computations on carboxylic acids endeavour to describe quantitatively the changes induced in the monomers by H-bonding. This concerns the changes in geometrical parameters, atomic charges and the quantities connected with them, force constants and energies of H-bonding. One of the most exciting dynamical problems approached both by quantum-chemical computations and experimentally is the proton transfer within the dimers. In the earlier computations, reviewed by Murthy and Rao[206], semiempirical methods, particularly CNDO/2 were used, but this was soon followed by *ab initio* methods. Most of the computations have been made on the formic acid dimer. Schuster's calculations[207], using the CNDO/2 method, consider the energy differences between the different

geometries and association patterns of formic acid. The energy of a single H-bond is the same in the conformation corresponding to the closed dimer as it is for the open dimer. This does not explain the preference of formic acid to form chains in crystal or in the pure liquid. However, the cooperative effect of H-bonding, demonstrated by the increased stabilization relative to isolated dimers, shows up in the calculation by Kertesz and coworkers made on the α-form of formic acid using the *ab initio* crystal orbital method[208]. The energy per H-bond in the chain was twice that of the dimer which is probably exaggerated. The energy for the β-form was less than for the dimer and improbably small.

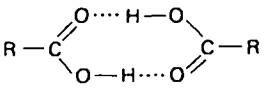
The lengthening of the C=O bond and shortening of the C—OH bond, along with a lengthening of the CO—H bond on approaching two monomers to form the dimer, are qualitatively correctly reproduced by Flood's *ab initio* calculation[209]. In this and other calculations the atomic charges change on H-bonding as expected from the general theory of H-bonding, i.e. the charge on the oxygens increases whereas it decreases on the hydrogen. Of course, the concrete figures depend upon the method used. The calculation of Almlöf and Martensen[210], using the iterative extended Hückel method, yields a nice pictorial representation of the differential electron densities of formic and acetic acids in which a slight charge accumulation turns up in the H-bond region. In the latest calculation of Iwata and Morokuma[211] the dissection of the stabilization energy in various contributions is given. The electrostatic component (−34.4 kcal/mol) is almost exactly compensated by the exchange repulsion energy so that the net effect (−17.5 kcal/mol) corresponds to the sum of the charge-transfer and polarization energies (−17.9 kcal/mol). The stabilization energy in this and other *ab initio* calculations[209,212] tends to be larger than the experimental ΔH_d^0 (Section II.D), but comes close to it when the quality of the basis set is improved. Iwata and Morokuma's calculation[211] also considers the electronic excited states and the ionization potentials. It turns out that H-bonding in the excited states is weaker. A rather flexible basis set was used by Bossi and coworkers[212] in a study the principal aims of which were the force constants. The problem considered is of dynamical nature and is the very large (~50 cm^{-1}) difference between the infrared and Raman active modes of the dimer. The calculation led to a large C=O/C=O coupling term in the vibrational potential energy, which is due to the dynamical charge transfer from one molecule to the other through the H-bond. The optimized geometry in this calculation is well within the limits of the experimental values and so is the stabilization energy.

Although the CNDO/2-computed stabilization energies of acetic, trifluoroacetic and trichloroacetic acids[213] are definitely too large (which is the well-known fault of the method), the relative energies do reflect the expected inductive effect. The negative effect results in a decrease of the basicity of the carbonyl group and an increase in the acidity of the hydroxyl group. The former effect is dominating and thus the energies of stabilization decrease in the order $(CH_3COOH)_2 > CF_3COOH.CH_3COOH > (CF_3COOH)_2$.

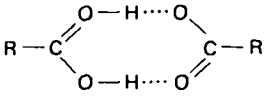
Using the same method, electronic charges of several carboxylic acids were computed by Momany and coworkers[214] for the purpose of constructing empirical intermolecular interaction potentials which may be used in the calculation of packing configurations and lattice energies of crystals. A density of states plot was calculated for the formic acid crystals by the CNDO/2 method. H-bonding strongly disperses certain molecular levels[215]. The electrostatic energy in the formic acid crystal has been computed using *ab initio* calculated multipole and point-charge sums[215a].

The intradimer proton exchange may be imagined as proceeding via dif-

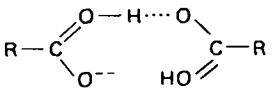
ferent processes or steps each of which are characterized by a different potential function. Calculations of these potential functions have been made by the CNDO/2 method[207,216] and at different *ab initio* levels[21,217]. For the single proton transfer[21] 2a → 2b the potential function shows only an inflection, whereas the simultaneous transfer 2a → 2c, in which the geometry of the acid residues remains frozen, is characterized by an asymmetric double minimum curve. The very appearance of a second minimum, the difference between the energy minima and the height of the barrier depend on the O . . . O distance[217] and, quite heavily, on the quality of the basis set[21,217]. This is also true of the barrier in the process in which the 'transition state' can be symbolized by 2d. Here the geometry of the acid residues is relaxed throughout. Using a small basis set, Del Bene and Kochenour[217] obtained a barrier height of 56 kcal/mol for the experimental distance 2.73 Å and 23 kcal/mol for the optimized distance of 2.54 Å. These figures show that the simultaneous proton transfer is easiest during the molecular vibration which brings the oxygens closest.



(2a)



(2b)



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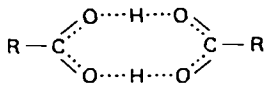
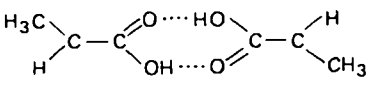


(2d)

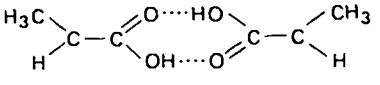
The computed barrier for the proton transfer should be comparable to experimental figures. The barrier for mixed dimers was estimated to be less than 14 kcal/mol from microwave data of Costain and Shrivastava[218]. The proton tunnelling appears to be faster than the overall rotation period of the dimer. However, the lack of isotope effect on the dipole correlation function, obtained by Fourier transformation of the far infrared band of the σ_{OH} vibration, indicates that the proton tunnelling frequency must be lower[219] than 10^{12} s^{-1}. The lack of isotope effect on the dielectric dispersion of acetic acid in benzene solutions is also taken as evidence against the existence of rapid tunnelling[220]. The infrared overtone region of formic and acetic acid solutions has been interpreted in terms of the splitting of OH stretching levels due to proton tunnelling and a potential barrier of 0.82–0.86 eV was deduced[221]. Although this is in rough agreement with the microwave results, the fitted potential function is only one-dimensional and the agreement may therefore be fortuitous. Thus the situation is not clear and further investigations are desirable.

The evidence for intradimer proton motions in crystalline carboxylic acids stems from consideration of the C=O and C—O bond lengths. If the protons are ordered the respective bond lengths should differ by rather more than 0.1 Å, as in the example of trichloroacetic acid[41]. The C—COH angles and C—C=O angles should also be different. With completely disordered protons the differences should disappear. An equal number of both tautomers may be expected if R(2a–c) do not cause any energetic preference for the proton position. *Cis–trans* isomerism with respect to the carboxyl group and the crystal environment may cause an energetic preference for one site. In fact the differences between the C—O bond lengths (Δr) and between the angles ($\Delta\theta$) vary from 0.1 Å to zero and from ~14° to zero[222]. The

linear correlation of Δr and $\Delta\theta$ is good evidence of the disorder[223]. An interesting case is that of fluoromalonic acid[224]. At room temperature the Δr is practically zero, but at liquid nitrogen temperature Δr is 0.07 Å. A temperature-dependent intensity change of some bands in the infrared spectra of solid normal fatty acids has been explained in this way[225]. *Cis* rotamers (**3a**) are more stable in odd-numbered fatty acids. At room temperature both rotamers coexist in propionic acid, but below 120 K the bands due to the *trans* rotamer (**3b**) disappear[226].



(3a)



(3b)

The study of the overall motions of carboxylic acids in the liquid and liquid-crystalline phases is still at the development stage. The most useful approach is the measurement of the spin-lattice relaxation times. Since two major types of processes contribute to this – breaking of the H-bonds and the overall rotation diffusion – and, since moreover, each of them is complex and involves monomers as well as various aggregates, their separate contributions have to be evaluated. Selective deuteration and independent data, particularly on association equilibria, as well as comparative investigation of relaxation characteristics of similar, but non-H-bonded molecules, are required for this. An investigation of the phase transition of the liquid crystalline *p*-hexylbenzoic acid in parallel with benzoic acid has shown[227] that the formation and destruction of H-bonds are strongly coupled to orientational motions of the molecules. In other words, the life-times of the various H-bonded configurations are controlled by the collective fluctuations of the molecular orientations. This investigation is based on the temperature and frequency dependence of the deuterium quadrupolar spin-lattice relaxation rate. In a preliminary study[228] of specific temperature-dependent ^{13}C spin-lattice relaxation times of several carboxylic acids a low activation energy for the relaxation process (~2 kcal/mol) was found. This is too low to be associated with H-bond breaking and must be due to an overall molecular reorientation.

A study of the molecular motion in the plastic crystalline and liquid phases of pivalic acid using Rayleigh scattering yielded the activation energies for the molecular reorientation during which the H-bonded dimers persist in all phases[229].

D. Thermodynamics and Kinetics

1. Dimers

Since extensive compilations of data on dimerization constants K_d, enthalpies ΔH_d^0 and entropies ΔS_d^0 exist[1b,1f,2e], we shall review only the present state of affairs concerning correlations with substituent effects and acidities. It has to be emphasized at the very beginning of this section that the differences in the experimental data are, to a large extent, of the same order of magnitude as the structural effects and there are very few systematically collected data where meaningful comparisons are possible.

The thermodynamic quantities obtained by different authors, even if using the same method, may vary considerably, e.g. the ΔH_d^0 values for propionic acid are given as between 15.1 and 18.0 kcal/mol. Therefore, in considering substituent and medium effects, one is limited to data from a single author. With a better

knowledge of the sources of errors, however, results are becoming more reliable. Evaluations of measuring techniques and computational procedures are given for the infrared method in References 230 and 231, and for n.m.r. in Reference 232. In computing the thermodynamic quantities it is generally assumed that at concentrations below 10^{-3} M it is sufficient to consider only the dimer–monomer equilibrium. The equilibrium between open and closed dimers has been considered in one investigation only and the equilibrium constant seems to be very small in dilute CCl_4 solution[233]. However, Bulmer and Shurvell conclude, from the band analysis of the ν_{OH} band of acetic acid, that at least four types of association are in equilibrium in the concentration range $10^{-2}-10^{-4}$ M in CCl_4[234].

As a typical value of $-\Delta H_d^0$ for the fatty acids 15 kcal/mol (7.5 per H-bond) may be taken. For instance, $-\Delta H_d^0$ for acetic acid determined from the peak height of the infrared monomer ν_{OH} band is 14.6 ± 0.5 and from the band area 14.8 ± 1.0 kcal/mol[231]. From the Raman intensity of the ν_{C-C} band of the dimer it is 15.50 kcal/mol and from the monomer 14.7 kcal/mol[235]. This gives an illustration of the quality of the recent determinations. It is pleasing to find, at least in this case, an excellent agreement with the older infrared results[236,237].

The effect of substituents is usually discussed in terms of changing the acidity of the OH group and the basicity of the C=O group. Thus the small differences in $-\Delta H_d^0$ between formic (14.8 kcal/mol) and isobutyric acids (15.2 kcal/mol) are attributed to the compensation of the inductive effects on both groups, i.e. the increased basicity of the carbonyl and decreased acidity of the OH[231]. The longer-chain fatty acids[133] show a slight decrease of tendency to dimerization in CCl_4 which is obviously not due to electronic effects.

It might be expected that the inductive effect would exercise a more pronounced effect in the halogenated acetic acids and the low dimerization constant of trichloroacetic acid in CCl_4 has been taken as an example[238]. ΔH_d^0 for trichloroacetic acid in CCl_4[239,240] is about the same as for acetic acid, although some authors find lower values[238], but the entropy is very high which might explain the low dimerization constant. Trifluoroacetic acid has been found in an infrared investigation[231] to have, in the gas phase, practically the same value of $-\Delta H_d^0$ (~15 kcal/mol) as acetic acid. Lower values were found by the n.m.r. method[176] and they appear to be reliable. Moreover, this is also in agreement with CNDO/2-calculated energies of stabilization[213]. However, no net influence of halogens on $-\Delta H_d^0$ has been found in an ultrasonic absorption investigation of the kinetics of association of halocarboxylic acids[241]. The considerable differences in equilibrium constants were attributed to entropy effects. Substituent effects in benzoic[242,243] and phenylacetic[233] acids have also been investigated by the infrared method. In the former series the effects are very small but particularly in the phenylacetic acid series, the effect of the negative substituent is to decrease K_d and increase $-\Delta H_d^0$ so that the Hammett equation can be applied.

The well-established linear relationship in H-bonded systems between ΔH^0 and ΔS^0 holds in the case of dimerization too, with the exception of the very strong trichloro- and trifluoroacetic acids[233].

The thermodynamics of heterodimer formation between aliphatic and halogenated aliphatic acids in CCl_4 has been investigated by infrared spectroscopy, vapour pressure and by calorimetry[238,244-246]. Results obtained by all these methods and also by microwave spectroscopy in the gas phase[218] indicate that mixed dimers are thermodynamically favoured, which is also in agreement with theoretical predictions[213].

The effect of the medium has been examined by several authors[247,248]. As in

other H-bonded systems the K_d and ΔH_d^0 decrease in the order gas phase > cyclohexane > CCl_4 > benzene. A lucid discussion of solvent effects on the thermodynamics of H-bonded systems in general may be found in Reference 248a.

Proton-accepting solvents are expected to lower the dimerization constants mainly by the competing effects of H-bond formation and carboxylic OH group liberation[248b], but the influence of the dielectric constant is certainly of importance[249]. The considerably lower K_d in benzene can be ascribed to OH π-bonding, the existence of which is demonstrated by the low frequency shift of the ν_{OH} band[250]. Solutions of acetic acid in acetone, acetic anhydride and dioxane have been studied by n.m.r., and from the dilution changes of the chemical shift, equilibrium constants for dimerization and monomer–solvent association constants were calculated[251]. Although the latter is largest for the acid–dioxane system (1.0×10^2 m.f.$^{-1}$) the acid dimerization constant is also highest in this solvent (4×10^3 m.f.$^{-1}$). The basicity of solvents is in the order dioxane > acetone > acetic anhydride, but this order does not correspond to the chemical shifts. The calculation is based on several simplifying assumptions of which perhaps the most questionable is the exclusion of a closed–open dimer equilibrium and also of the open dimer–solvent equilibria. The importance of these equilibria has been stressed in an investigation of the kinetics of H-bonding in the acetic acid–acetone system using the ultrasonic absorption method[252]. Accordingly a two-state model has been used to calculate the kinetic parameters.

In general it is assumed that the stronger the acid the less is the tendency to dimerization[253]. This is in agreement with the theoretical result[213] that the negative substituent effect on the carbonyl charge (reduction) will predominate over the enhancement of acidity of the OH group. However, considering the essential difference in the processes of ionization and H-bond formation, including also the role of solvation, it is difficult to expect a simple relationship between the pK_A of acids and their K_d or ΔH_d^0 values. The classification of carboxylic acids into three types (benzoic acids, saturated and acetylenic acids, phenylacetic acids) by Goulden[253a], following their ν_{OH}–pK_A relationships, is well known. However, in correlating the ν_{OH} and K_d of these acids a single straight line is obtained[233], which also demonstrates the difference in character of the two processes and their sensitivity to structural effects.

The mass effect on the stability of the H-bond is an often discussed question. Considering the zero-point vibrational energy the D-bond should be more stable. In fact $-\Delta H_d^0$ for benzoic acid-d, exceeds by more than 1 kcal/mol the value for the normal acid[254].

Several investigations of the kinetics of dissociation of H-bonds in acid dimers using the ultrasonic relaxation methods have followed the first application of this method by Maier[255]. Since several relaxation processes are concurring it is not a simple matter to distinguish between them and it is necessary to measure at various frequencies and temperatures. Besides the rate constants of the forward and reverse reactions enthalpies and entropies of activation are obtained and also the ΔH^0 and ΔS^0 of H-bonding. An important point is that the ultrasonic absorption is usually measured on pure liquids or in polar solvents and the main relaxation process may be attributed to the rupture of a single H-bond. Thus it is interesting to note that the $-\Delta H^0$ values (of the order of 4.5 kcal/mol) are very similar to those obtained from spectroscopic investigations in dilute solutions, where the calculated thermodynamic quantities pertain to the monomer–dimer equilibrium.

Data for acetic[256], propionic[257] and several substituted benzoic[258,259] acids, and for halogen carboxylic acids[241], are available. For a series of aliphatic carb-

oxylic acids the $-\Delta H^0$ of H-bonding in pure liquids has been found to increase with the number of hydrogen atoms substituted by carbons and the effect is correlated with Taft's σ constants[260]. However, the enthalpy of activation ΔH does not correlate with σ. In the series of substituted benzoic acids in DMF the correlation of ΔH with σ was established and a value of 1.22 for the dissociation, and $X = -0.33$ for association, were found[258]. Different values were obtained in an earlier investigation[259]. It is interesting to note that the influence of substituents on the thermodynamic quantities appears more pronounced in data obtained by the ultrasonic method than in those obtained from spectroscopic work. Apart from possible systematic errors the differences may be due either to the different conditions (pure liquid or polar solvent in the first case, gas or dilute non-polar solution in the second), or to the difference in the basic reaction (closed–open dimer transition in the first, dimer–monomer equilibrium in the second), or to both factors.

2. *Carboxylic acid hydrates and other molecular complexes*

Amongst complexes of carboxylic acids with bases the hydrates are certainly most important. The existence of dimer and monomer mono-, di- and trihydrates in non-polar solvents has been inferred from partition of carboxylic acids between the organic and aqueous phases[261]. The formation of such hydrates is the reason for, apart from the influence of changing the dielectric constant of the solvent by the water content, low dimerization constants obtained by the partition method[262]. In a recent study of partition of a series of carboxylic acids between water and benzene, the hydration constants, and hydration numbers of the lower fatty acids and halogenated acids, were determined and the dimerization constants corrected for hydration. The K_d thus corrected agree with those obtained by spectroscopic methods[263]. Dimerization constants of several carboxylic acids obtained from partition between organic solvent and the aqueous phase are given in two Russian papers and discussed in terms of the influence of the solvent dielectric constants and hydration[264,265]. Heats of solution in water and chloroform are reported by Lakhnapal and coworkers[266] for mono-, di- and trichloroacetic acids. In view of the many factors of both endo- and exothermic character it is difficult to relate their data to the H-bonding between acid and water molecules. Association equilibria of the lower aliphatic carboxylic acids and their hydroxy derivatives have also been studied by ultrasonic interferometry[267].

The association of carboxylic acids with stronger bases has also been studied, though less extensively. From a dilution study of several lower fatty acids and trifluoroacetic acid by dimethylsuphoxide (DMSO) based on proton chemical shifts, 1 : 1 and 2 : 1 acid–base complexes were postulated and the formation constants calculated[268]. The thermodynamic quantities of association of mono-, di- and trichloroacetic acids with a series of oxo bases were determined in very dilute CCl_4 solution using both the infrared[269] and ^{1}H n.m.r. methods[13]. The weakest base was DMSO and the strongest pyridine *N*-oxide. The increase in ΔH^0 corresponds roughly to the relative acidities and basicities, respectively and the highest attained value is 24 kcal/mol. However, this highest value is obtained for the trichloroacetic acid/trioctylphosphine oxide complex and about the same for the complex of this acid with pyridine *N*-oxide although the latter is more basic and displays both a lower shielding and larger $\Delta\nu$. Very large ΔH^0 values have been found[270,271] for the homoconjugate ion $(CH_3CO_2HO_2CCH_3)^-$ in acetic acid (~25 kcal/mol) and for the complex $CH_3COOH\,..\,F^-$, also in acetic acid

(~29.5 kcal/mol). It is interesting to note that an *ab initio* calculation of the stabilization energy of this complex has given a higher value than for $(FHF)^-$ which is the strongest known H-bonded system[272].

The carboxylic acid–nitrogen base complexes in pure liquid state or solution present interesting problems concerning both the molar ratios and the proton transfer. A considerable number of investigations of these systems have been made using mainly dielectric methods[273,274], but infrared[275–277], n.m.r.[278] and u.v.[279,280] spectroscopy and calorimetry[281] have also been exploited. In carboxylic acid–amine solutions both 1 : 1 and 2 : 1 complexes exist as shown by dielectric titrations[282]. It is interesting to note that the polarity in the 2 : 1 complexes is enhanced in comparison with the 1 : 1 complexes. Apparently in the —COOH–amine complex the addition of a second acid molecule favours the proton transfer so that ion pairs are formed to a larger extent than in the 1 : 1 complexes. Although in principle the steric arrangement of molecules in a complex can be deduced from dipole moments this is more difficult for the carboxylic acid–amine complexes because of the considerable induced dipole moment in the complex and the equilibria between the neutral and ionic species. In fact, the latter must be determined by independent methods before the proposed structure can be trusted.

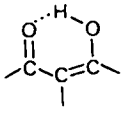
Enthalpies of H-bonding have been determined by infrared spectroscopy[275] for a series of complexes between acetic and chloroacetic acids, and several substituted pyridines in CCl_4. The $-\Delta H^0$ values vary between <1 kcal/mol and 9.8 kcal/mol depending on the relative acidities and basicities expressed by the pK values. With the stronger acids and bases proton transfer occurs and the determination of the thermodynamic quantities does not extend to this side. The ΔH^0 values obtained with the pyridine bases are much lower than with the oxo bases relative to their basicities expressed by protonation constants[275].

The formation of acid–base complexes in 1 : 1, 2 : 1 and even 3 : 1 ratios has recently been followed by the partition method (water–benzene) for several fatty acids and substituted pyridines. A linear free-energy relationship between the formation constants and the protonation in water of the bases has been established[283].

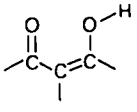
Formation of homoconjugate ions $BH^+ HX_2^-$ in the reaction between carboxylic acids and amines in hexane has been postulated from differential vapour pressure and i.r. data[284]. Investigations of H-bonding and proton transfer kinetics in carboxylic acid–amine systems were recently reviewed by Bureiko and coworkers[285]. Proton-transfer kinetics in aminobenzoic acids have been studied by the ultrasonic method[286].

E. Intramolecular H-Bonding in Carboxylic Acids

With appropriate steric arrangement of donor and acceptor groups intramolecular H-bonds will be formed. The optimal configuration occurs in the 6- and 7-membered chelate rings (4a) where both the bond angles and the electronic configuration of the conjugated system warrant maximal H-bond strength. Typical examples of this type of bonding are found with salicylic acid and its derivatives[287,288]. Quantum-chemical treatments have been centred on the simpler case of malonaldehyde[289,290], but the results can be sensibly applied to the former type of compound. The difference between the conjugated (chelated) H-bonded ring and one containing sp^3-hybridized carbon shows up in the calculations of H-bond energies (CNDO/2) of malonaldehyde and β-hydroxypropionaldehyde[289].



(4a)



(4b)

In this calculation the H-bond energy is defined as the difference between the *cis* (**4a**) and *trans* (**4b**) configurations. The former is about three times larger.

An experimental comparison between *o*-aryloxy and β-hydroxylalkyl acids, which would demonstrate the role of the π-electron system, is not possible because the formation of a six-membered intramolecular H-bond is hindered by the repulsion of the CH_2 groups and, in fact, does not exist in β-alkylpropionic acids[291]. However, the role of the π-electron system is demonstrated by the difference in ΔH^0 between the isomeric 1,2- and 2,3-methoxynaphthoic acids[292]. The involvement of the π-electron system in chelation is also expressed in the electronic absorption spectra of *o*-alkoxybenzoic[293] and methoxynaphthoic acids and methyl hydroxynapthoates[292].

Five-membered rings are both sterically and electronically much less stable. For instance, $-\Delta H^0$ of intramolecular H-bonding of 2-methoxy-2-naphthoic acid is 2.69 kcal/mol and of pyruvic acid 1.67 kcal/mol (both in CCl_4), whereas for methoxyacetic acid $-\Delta H^0$ is only 0.67 kcal/mol[292]. It should be noted that the $-\Delta H^0$ values of pyruvic acids in the gas phase[294] are considerably larger (2.3–3.2 kcal/mol).

A seven-membered ring is formed in maleic acid. Thermodynamic parameters are not available but its shortness (2.502 Å) and near-linearity evidence the H-bond strength[58]. Some steric compression[295] may occur in the 7-membered rings in which eventually symmetrical H-bonds are possible. Examples were given in Sections II.A.1, II.B.1.b and II.B.2.

Intramolecular H-bonding plays an important role in the stereochemistry by stabilizing the conformation in which it occurs. The stable conformation of the free carboxyl group is hydroxyl *cis* with respect to carbonyl. The theoretically calculated difference (formic acid) is 6.3 kcal/mol[295a] and the experimental estimate is about 3 kcal/mol[296] the former being probably too large. Infrared and u.v. spectroscopic investigations have been made on α-keto and α-alkoxycarboxylic acids[297], *o*-aryloxybenzoic acids[293], ethoxynaphthoic acids[292], α-hydroxycarboxylic and *o*-hydroxybenzoic acids[288]. From all these studies it is obvious that the intramolecular H-bond strongly stabilizes the *trans* conformation in contrast to the unsubstituted acids. The strength of the bond as estimated from infrared ν_{OH} and $\nu_{C=O}$ is influenced by substituents and the electronic effects can be rationalized by their σ constants[288].

The experimental estimate of enthalpy of the intramolecular H-bond (~3.3 kcal/mol in *o*-methoxybenzoic acid[298]) reflects, besides the actual bonding process, the difference between the *cis* and the *trans* conformation of the carboxyl group. Taking this into account the difference between the dimer H-bond and the intramolecular H-bond is not large. Moreover, the entropic factor favours intramolecular bonding[299]. Thus intramolecular H-bonding may be competitive with dimerization in the equilibria. In fact, in α-keto acids the intramolecularly bonded form predominates over the dimeric one in non-polar solvents and at concentrations below 0.3 M[300] and the chelate form is also stable[294] in the gas phase up to 180°C.

In Section II.A.2 were described several crystal structures of substituted carboxylic acids which might form, in principle, intramolecular H-bonds as well as

either dimers or intermolecular carboxyl–substituent bonds. Although generalizations are difficult it appears that the carboxyl OH is involved in intramolecular bonding in the case of very strong acceptors only. Such strong acceptors are nitrogen (*o*-aminobenzoic acid)[117], *N*-oxides (pyridine-*N*-oxide-2-carboxylic acid)[301], and particularly, ionized carboxyl groups. The examples of acid maleates and 2,3-pyridine carboxylic acid have been mentioned before. However, even with such potential acceptors, intermolecular bonding may predominate[89], which shows that other factors besides the H-bond energy determine conformation and the association pattern in solids. The conformational energy of glycolic acid has been treated quantum-chemically[301a] and the planar, intramolecularly H-bonded conformer appears to be energetically strongly favoured. The theoretical results are set against X-ray structures of α-hydroxycarbonyl and related compounds and comparisons made between inter- and intramolecular H-bonding.

Intramolecular H-bonding affects physicochemical properties ranging from photoreactivity (e.g. azobenzene-*o*-carboxylic acids[302]) to acid dissociation constants. The acid dissociation constants of dicarboxylic acids have attracted most attention. The increased k_1 and decreased k_2 are attributed to the stabilizations of the acid monoanion by intramolecular H-bonding and the subject has been very lucidly reviewed by Eberson[303]. The strength of the H-bonding and hence the characteristic k_1/k_2 ratio depend particularly on the steric arrangement of both carboxyl groups. According to the model studies of McCoy[304] the groups should be spaced so that a linear intramolecular H-bond with $R_{O..O}$ of 2.45 Å can be formed without much strain on the carbon skeleton. Extensive investigations of dissociation constants of both aliphatic[75] and aromatic diacids in dipolar aprotic solvents[305] have been carried out. The relation between the dissociation constants and H-bonding and the role of substituents in malonic acids have been studied by n.m.r. spectroscopy[306].

The stability of the prototype intramolecular H-bond in acid maleate and phthalate in strongly proton-accepting solvents like water, dioxane and amines is also an interesting problem that has been approached by several authors[91,307,308]. A recent systematic study[309] shows that these bonds resist any solvent but aqueous diethylamine and piperidine.

Not only intramolecular H-bonding between two carboxyl groups is important for the dissociation constants but also bonding between other substituent proton donors in which the carboxyl group may be involved. This appears from studies of equilibrium constants of various H-bonded neutral and ionic species[310] of salicylic acid and the isotope effect on the pK of this acid[311]. The high pK_A of *N,N*-dimethylanthranilic acid has been connected[312] with the intramolecular H-bond, $\geqslant N^+-H \ldots OC(O)^-$, which is also postulated as existing in the solid[313] on the evidence of the infrared spectrum. However, in CCl_4 solution the spectrum indicates H-bonding without proton transfer, $\geqslant N \ldots HOC(O)^-$.

III. ESTERS, LACTONES, ANHYDRIDES AND ACYL HALIDES AS PROTON ACCEPTORS

Perhaps it is necessary to consider first the question of the site of proton acceptance in the first three groups of carboxylic acid derivatives since there are two such sites, the carbonyl oxygen and the singly-bonded oxygen. There is, in fact, no direct proof, but the now general acceptance of the carbonyl bonding is based

both on the analogy with protonation[314] and on solvent effects on the carbonyl group. Shifts of the infrared $\nu_{C=O}$ band in proton-donating solvents have been studied by Bellamy and Williams[315] and of the carbonyl ^{13}C magnetic resonance by Maciel and Natterstad[191]. However, Powell and West[316] have also considered the possibility of a competition for H-bonding between the two types of oxygen atoms.

The next question concerns the relative donor propensity of the carbonyl in these carboxylic acid derivatives. For this purpose the infrared frequency shifts and proton magnetic resonance shifts of proton donors, mainly phenols, as well as thermodynamic parameters of bonding, should be considered. Systematic studies, though of limited extent, have been carried out by the groups of Gramstad[317,318], Taft[319] and Lutskii[320]. Although the difference in $-\Delta H^0$ values for H-bonding between phenols and comparable esters, lactones and anhydrides are small (all fall within the range 4–5 kcal/mol), a comparison of available data arranges these carboxylic acid derivatives in the following order of decreasing acceptor propensity: γ-lactones > esters > β-lactones > anhydrides ⋙ acyl fluorides. The ranking of anhydrides is questionable since only the comparison of ethanol (and not phenol) bonding to ethyl-acetate and acetic anhydride is available[321]. Acyl fluorides[317] are considerably inferior proton acceptors, $-\Delta H^0$ being 2–3 kcal/mol. A rationalization of the substituent electronic effects in general on the H-bonding propensity of a carbonyl compound of the type X C(=O)CH_3 has been proposed by Taft and coworkers[319] using their pK_{HB} values (see Section II.D.2) and the σ_I and σ_R constants. H-bonding between esters of dicarboxylic acids $CH_3OCO(CH_2)_n$-$COOCH_3$ with $n = 0$, 1, 2, 4, 8 has been studied by Lutskii and coworkers[320]. They observed a gradual increase of $-\Delta H^0$ with n from 2.4 to 4.6 kcal/mol. The same authors[322] have also compared dicarbonyl compounds of the type YC(=O)-$(CH_2)_n$C(=O)Y, and the $-\Delta H^0$ values rank the Y substituents in the order $N(C_2H_5)_2 > CH_3 > OCH_3 > OCH{=}CH_2$, which is in agreement with other data.

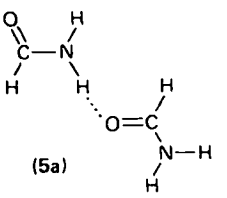
Infrared spectra of the methyl esters of C_{12-16} hydroxy carboxylic acids indicate differences in H-bonding depending upon the method of preparing the crystals. Intermolecular bonding seems to exist in crystals obtained from the melt and intramolecular bonding in solution-grown crystals[323].

IV. H-BONDING IN AMIDES

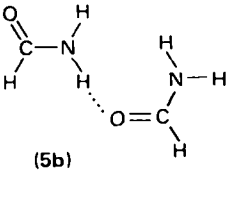
A. Theoretical

The earlier semiempirical calculations on H-bonding in amides, reviewed by Murthy and Rao[324], have now been added to by several *ab initio* studies. Their subject was mainly formamide in the closed dimer form, but the linear dimers and linear oligomers were also considered, and with respect to various mutual orientations[325,326]. Perhaps the most illustrative description of H-bonding in formamide emerges from two papers by Pullman and coworkers. The first[327] considers the electronic changes on H-bonding to a closed dimer and the second[328] the open dimer in two sterically different arrangements. An analysis of various contributions (electrostatic, charge transfer, polarization) to the H-bonding energy as a function of the CO . . . N distance and of the CO . . . H—N angle has been made[328]. Whereas a 'frozen' geometry of the formamide residue was used throughout these studies Ottersen and Jensen[329] have optimized the geometry and even calculated the force constants. In a subsequent study, Ottersen[330] has also considered the dimer of the enol form. The H-bond energies have been calculated for open and closed dimers

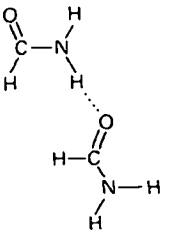
and for oligomers, allowing for differences in *cis–trans* isomers[331,332]. In all these studies, except the last one, two or more basis sets have been used comparatively. Disregarding the quantitative aspects of various basis sets the effect of H-bonding on the charge population of formamide shows that the general trends are as in other H-bonded systems, i.e. loss of charge from the H-bonding hydrogen and the carbonyl carbon, and gain on the carbonyl oxygen and on the proton-donating nitrogen. A more detailed analysis of the charge distribution in the linear open dimer is given by Dreyfus, Maigret and Pullman[327] and by Dreyfus and Pullman for the closed dimer[328] The optimization of the C=O, C—N and N—H bond lengths with respect to variations of the O . . . N distance shows that with increasing H-bond strength the C=O bond length increases and the C—N decreases, whereas the N—H bond lengthens, which is in agreement with the experimental results. The changes in geometry may be considered as an enhancement of the resonance in the CNO fragment by H-bonding. Although the calculated stabilization energies tend to be larger than the experimental ones and are strongly influenced by the quality of the basis set[333], the results obtained by using the same basis set allow definite conclusions as to the relative stabilities of various geometries. Thus, amongst the possible open dimers **5a–5d**, **5a** and **5c** are the most stable (8.3 and 8.2 kcal/mol),



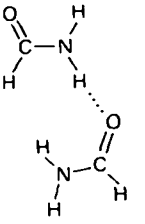
(5a)



(5b)



(5c)



(5d)

the others being by about 1 kcal/mol less stable[332]. The energy dependence of the angle θ at the optimized O . . . N distance of 2.85 Å shows a flat minimum between 45° and 75° and a shoulder for the linear arrangement[327]. At the STO-3G level[332] the H-bonds in the closed dimer (*cis* association) are stronger by ~1 kcal/mol than in the open one formed in *trans* association. However, with adding more molecules to form trimers to pentamers in the *trans* conformation the stabilization energy per one H-bond increases from 8.28 kcal/mol in the dimer to 10.42 kcal/mol in the pentamer. Larger cyclic mixed aggregates (*cis* dimer with two more *trans*-associated molecules) do not show the additional stabilization as in the all-*trans* chain. Although the absolute H-bond energies are exaggerated due to the method of calculation, the cooperative effect is real as will be shown in the following paragraph and is well substantiated by more sophisticated calculations on water[333].

Janoschek[334] has calculated the potential-energy surface for two variables (N—H and N . . . O distances) and the dipole-moment surface for the coupled motion of both protons in the cyclic formamide dimer. The potential has a deep, asymmetric minimum for each proton near its nitrogen. The infrared spectrum for the NH stretching was also calculated.

Scheraga and coworkers[335] have used their CNDO/2-computed charges of a series of amides to calculate the interatomic potentials. From these data they have derived models for association structures and, in a subsequent paper, the packing configurations in crystals, which agree reasonably with X-ray-derived structures[214]. Lifson and coworkers[336,337] have calculated the force fields for several amide crystals using both theoretical and experimental data. They have inferred that the role of H-bonding in the crystal packing is not much more important than the role of other intermolecular forces. Some information on the dynamics of the H-bond in the formamide crystal and liquid phase are available from Rotschild's[337a] dipole correlation functions which were derived from far-infrared spectra of Itoh and Shimanouchi[337b]. The phonons involved in the intermolecular motions have lifetimes of 0.6 to 0.8 ps.

B. Association in Solid Amides

1. *Secondary amides*

Since the favoured conformation of open secondary amides is *trans*, their typical association pattern is the zig-zag chain. *N*-methylacetamide[338] in its low temperature modification may be taken as representative both of the crystal structure and molecular parameters of the H-bonded amides (Figure 5). It is also appropriate for demonstrating the changes in the molecular bond lengths and angles. The data for the free molecule are available from a gas electron diffraction study by Kitano and coworkers[339]. The most interesting changes concern the amide C—N bond which is shortened by nearly 0.1 Å and the C=O bond which is lengthened by only about 0.01 Å. The N—C=O angle is slightly increased (>1°). The other orthorhombic modification which is stable between 10° and 28°C differs essentially in the size of the unit cell only.

Chloroacetamide[340] is interesting because it contains two types of H-bonded chains which form alternating layers. The molecules in each layer differ in the

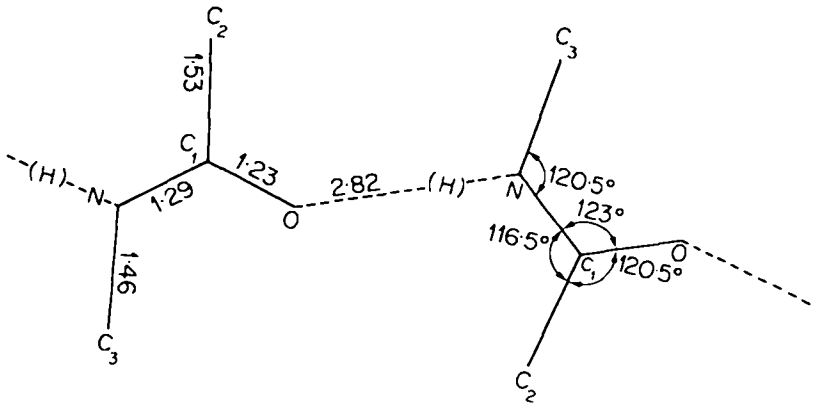


FIGURE 5. Molecular parameters of *N*-methylacetamide.

conformation of the chloromethyl group and the NH . . . O distances. In the chains formed by molecules with all heavy atoms in one plane the NH . . . O distance is 2.81 Å whereas in the chains formed by slightly twisted molecules the distance is 2.77 Å. This difference illustrates the influence of non-bonded interactions on the H-bond which is in most cases about 2.85 Å long.

Lactams of eight carbon atoms and more (e.g. caprylolactam[341]) are flexible enough to assume the transoid conformation of the amide group and associate to chains, with the usual NH . . . O distance being 2.86 Å. The pelargolactam molecule[342] can exist in various conformations giving rise to different types of ordered H-bonded chains, but these then associate in a disordered way. The cisoid configuration of medium-size lactams leads to ring dimer association, e.g. ε-caprolactam[343]. The bonds in the centrosymmetric dimers are 2.90 Å long. Substituted glutarimides also form H-bonds around centres of symmetry[344]. However, glutarimide[345] associates by overlapping zig-zag chains through rather long H-bonds (2.94 Å). Succinimide again forms the usual centrosymmetric dimers[346].

2. *Primary amides*

The availability of two protons for H-bonding increases the possibility for association to different types of networks. The fundamental unit in most primary amide crystals is the centrosymmetric dimer. The rather precise structure of sorbamide[347] may be taken as an example (Figure 6). Following the requirements

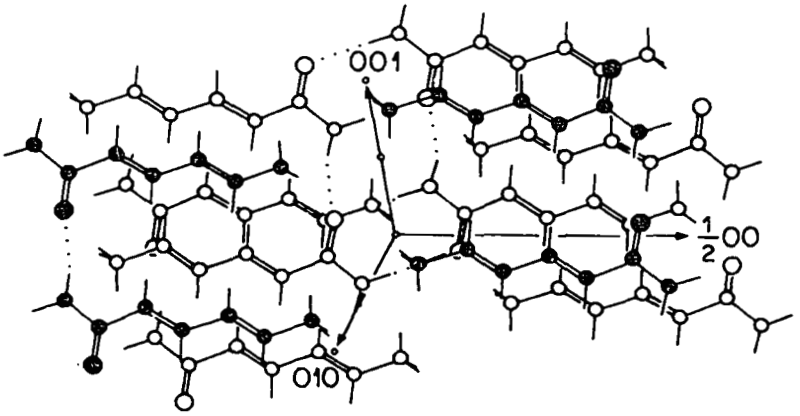


FIGURE 6. X-ray structure of sorbamide. Reproduced with permission from S. E. Filipakis, L. Leiserowitz and G. M. J. Schmidt, *J. Chem. Soc. (B)*, 297 (1967).

of maximal electrostatic attraction between the NH hydrogen and the oxygen inner (*cis*) lone pair, the H-bonds in the dimer should be collinear. Although the theoretically calculated potential energy surfaces[328] show a very flat minimum, the departures from the 180° N—H . . . O angle are usually very small, e.g. difluoroacetamide[348] and cyanoacetamide[349]. Non-centrosymmetric dimers are very rare. One example is adipamide[350] and another is cyclopropenecarboamide[351]. In the orthorombic form of acetamide[352] and in cyanoacetamide[349] the dimers are pseudo-centrosymmetric. Through the second NH_2 hydrogens and the oxygen lone pairs of neighbouring dimers interdimer H-bonds are formed connecting the dimers

into endless ribbons. Very often the interdimer H-bonds are shorter than the intradimer bonds as for example in formamide[353] (2.880 and 2.935 Å). A prominent example is dibutylacetamide[354] where the chain H-bond is only 2.852 Å and the intradimer bond 2.967 Å. Moreover, the chain packing is the same as in *N*-propyl dipropylacetamide[354]. This may suggest that the interdimer bonds are in fact stronger and, consequently, chains as in secondary amides may be considered as the primary association pattern. Furthermore the H-bonds in chain-associating transoid lactams are shorter than in the ring dimers of the cisoid lactams[341,342]. However, the departures from colinearity of the interdimer bonds and of the NH . . . O angle, being much less in for example benzamide[355] than 180°, corroborate the inference that the dimer bonding is stronger. There are examples where the interdimer bonds are very long, even to the extent that it is difficult to consider them as H-bonds, e.g. δ-pyrazincarboxamide[356]. The second NH may be involved in intramolecular H-bonding as in 1-methyl-1,4-dihydronicotinamide[357] and only the dimers are then formed. At any rate, it appears idle to discuss the primary association structure in terms of the relative strength of H-bonds, because the H-bonds are only one of the factors determining the packing pattern, and in any case they are not very strong in amides.

Packing modes of the dimeric units have been rationalized by Leiserowitz and Schmidt[358]. Three main types are considered: (*i*) glide-plane packing in which the dimers are connected by interpair H-bonds into ribbons; the molecules are flat and related by glide planes; (*ii*) screw-axis packing in which the amide groups are no longer coplanar, and (*iii*) translational packing which differs from (*i*) in that the angle between the mean molecular plane and the glide plane of (*i*) is reduced to zero.

The packing pattern depends upon the competition of factors assuring the maximum of H-bonding stabilization (maximum number of H-bonds and minimum of potential energy with respect to variation in H-bond angles) and the non-bonded interactions between radicals and amide groups, respectively. The packing modes (*i*) to (*iii*) are idealized and real systems will depart from them, particularly because of the last mentioned type of interatomic interactions. For instance, in the ideal case the molecular plane should be at 90° to the glide plane in type (*i*) packing. This is so in succinamide[359], but in fumaramide[358] the angle is 70° and in crotonamide[360] 61.5°.

Polymorphism is quite common amongst amides and may be connected with differences in packing patterns. The most striking example is acetamide which exists in orthorhombic and trigonal forms. In the orthorhombic form[361] there is the usual association to sheets with the glide-plane type of packing (*i*) whereas the H-bond network of the trigonal form[362] is three-dimensional and so far unique amongst amides. Pyrazincarboxamide has four modifications[363]. In the α-[364] and β[365]-forms the interdimer bonds are already very long (3.14 and 3.17 Å, respectively) whereas in the δ-form[356] the N–H . . . O contact exceeds even the sums of the van der Waals' radii. The structure of the fourth modification is not known.

3. Amide hemihydrohalides

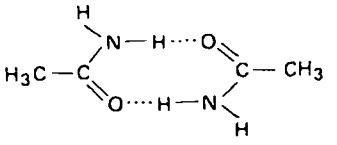
By analogy with acid salts of carboxylic acids (Section II.A) extremely short H-bonds exist in the complexes of two amide molecules with one molecule of halogen hydride. The diffraction study of acetamide hemihydrochloride[366] shows that the proton bonds two amide units by their oxygen atoms at a distance of 2.42 Å. Similar structures have also been obtained for acetamide hemihydro-

bromide[367] and the hemihydrochlorides of caprinolactam[368] and pelargolactam[369]. The vibrational spectra of acetamide hemihydrochloride bear the same general features as the spectra of the acid salts of carboxylic acids of type A[370].

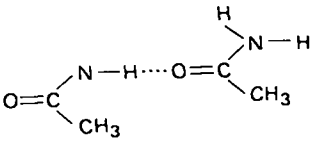
C. H-Bonding of Amides in the Liquid State

1. *Self-association*

Structural and thermodynamic aspects of amide association in the liquid phase are intimately connected with their conformation. The simplest cases are the small-ring lactams in which the *cis* conformation is fixed. This conformation favours the formation of ring dimers (**6a**) that is typical of *cis* conformed amides in general.



(6a)



(6b)

Similarly to carboxylic acids the closed dimer is more stable, not only because of the two H-bonds, but also because the stabilization energy per bond exceeds that in open *trans* dimers[332]. However, the existence of open dimers (**6b**) or even polymers has been postulated for the pure liquid caprolactam[371] from the evidence of the characteristic ν_{NH} and γ_{NH} frequencies (ring-dimer association: ν_{NH} 3218 cm^{-1}, γ_{NH} 800 cm^{-1}; open dimer or chain association: ν_{NH} 3300 cm^{-1}, γ_{NH} 670 cm^{-1}). These frequencies are useful for differentiation between the two types of association.

The most investigated example is ε-caprolactam and the enthalpy of association has been determined by various methods. The values of $-\Delta H_d$ per H-bond range from 2.8 kcal/mol[372] to 6.8 kcal/mol[373]. δ-Valerolactam appears to have stronger H-bonds. N.m.r determinations in CCl_4 yield $-\Delta H_d$ (two H-bonds) between 8 and 9 kcal/mol[374] and infrared yields 7.1 kcal/mol[375] and even 10 kcal/mol[376] with a large solvent effect. The difference between ε-caprolactam and δ-valerolactam might be due to the difference in ring strain, but the scarcity and quality of the data precludes any further attempts at correlating structural effects on H-bonding.

The association enthalpies are strongly influenced by solvents. Those with higher dielectric constant diminish $-\Delta H^0$. Lazniewski and Mokrzan[377] have determined calorimetrically the heats of dimerization of caprolactam in five solvents and obtained a linear dependence of the heat and dielectric properties as required by Davies and coworkers[378].

Ring-dimer formation is not possible with the *trans* conformation which is the stable form of simple open secondary amides such as *N*-methylacetamide. This type of amides can form open dimers (**6b**) and larger chain associations. The ν_{NH} frequency of self-associated *trans* amides (3300 cm^{-1}) indicates weaker bonding than in the ring dimers. Dementyeva and collaborators[379] claim that this frequency difference is not connected with conformation itself but only with the strength of bonding since both the small and the large ring lactams (*cis* and *trans* conformation) and open *trans* amides have similar ν_{NH} frequencies when H-bonded to the same proton acceptor (e.g. *N*-methylpyrrolidone). The greater tendency to ring-dimer

formation of open secondary *cis* amides has been demonstrated by Andrews[380] with formanilide and *o*-methylformanilide in which both forms coexist in CCl_4 solution. At high dilutions (~0.002 M) the *trans* population is monomeric whereas *cis* association persists. These results are in agreement with the earlier qualitative n.m.r. observations on formanilide[381]. The *cis* dimerization constants for *o*-methylformanilide (at 20°C) of 304.8 and 132.5 l mol^{-1}, respectively, were determined by infrared techniques. These constants are larger than the dimerization constants of, for instance, acetamide by at least one order of magnitude.

Most of the studies of self-association have been done on the more common *trans* form. The outstanding characteristic is the tendency to higher association as predicted by quantum-chemical calculations[332]. The equilibrium constants for *n*-merization are about ten times larger than the dimerization constants. The constants for trimerization and higher association probably vary, but this is practically impossible to deduce from experimental data. Thus only the dimerization constant (K_d) and an average polymerization constant ($\bar{K}$), or even only one constant, are introduced in the treatment of experimental data. On top of the difficulties in determining accurate thermodynamic quantities from spectroscopic data, as in the case of carboxylic acids, the n.m.r. approach is complicated by the ^{14}N quadrupole broadening of the NH signal. Nevertheless, the most recent collection of thermodynamic data of secondary amides has been obtained by this method[382]. *N*-Methyl-, isopropyl-, and *t*-butylacetamides in CCl_4 have been investigated. The experimental data were treated in terms of K_d and $\bar{K}$ to describe the higher association steps. The latter is 10 to 16 times larger than K_d depending upon the *N*-substituent. The increased strength of chain association is also reflected in larger $-\Delta\bar{H}^0$, but the entropy also favours higher association. The decrease in association tendency with increasing size of the *N*-substituent appears to be of steric origin, a conclusion which is in agreement with the earlier infrared work of Jones[383]. The $-\Delta H_d{}^0$ and $-\Delta\bar{H}^0$ values of 3.7 ± 0.3 and 4.5 kcal/mol, respectively, are in reasonable agreement with earlier results[384,385] considering the difference in the methods and treatments of experimental data. However, in a fairly recent n.m.r. study of self-association of *N*-methyl- and *N*-ethyl-acetamide, and of *N*-methylpropionamide, $-\Delta H^0$ values of the order of 7 kcal/mol were obtained, using only one equilibrium constant in the calculations[386]. These values seem to be excessive. Lowestein and coworkers[387] have determined by infrared spectrophotometry the thermodynamic parameters of self-association in CCl_4 of *N*-methylacetamide and its deuterated analogue. A difference of 0.5 kcal/mol was noted. The $-\Delta H^0$ of the deuterated amide was smaller.

An interesting detail noted in Reference 382 is the temperature dependence of the chemical shift of the free NH-proton which might be connected with a shift in the population of the two possible, but energetically different, dimer structures which were predicted from theoretically calculated interatomic potentials[335]. In the dimer with lowest energy the monomers are aligned in such a way as to bring the acetyl protons of one molecule and the *N*-methyl protons of the other into close proximity. In the second configuration the acetyl–acetyl and *N*-methyl–*N*-methyl interactions dominate in both monomers. Although a rationalization of the observed shifts in the series of *N*-alkylamides is possible along this line, the interference of solvent and other effects cannot be readily eliminated.

The thermodynamic parameters of H-bonding of secondary amides have also been determined in dioxane solution[388]. The very small $-\Delta H^0$ values reflect in fact the difference between the amide–amide and amide–dioxane bonding energies. The ^{14}N chemical shifts of formamide and *N*-methylacetamide in dioxane and

several other solvents, both proton-donating and -accepting, were measured by Saito and coworkers[389]. The ^{14}N shifts correlate with the ^{1}H shifts and this was discussed with respect to the electric field effect of H-bonding, but no thermodynamic parameters were derived.

The general rule that $\bar{K} > K_d$ and $-\Delta\bar{H}^0 > -H_d{}^0$ appears to be broken by *N*-methyltrichloroacetamide, the H-bonding of which (in benzene) leads to a monomer $\rightleftharpoons$ dimer process[384]. In this respect it equals the primary amides in which the dimerization is also dominant.

The primary amide NH_2 group offers several possible ways of association, but the formation of cyclic dimers appears to be preferred, at least in dilute solution. However, sedimentation equilibrium studies[390] of self-association of *N*-methylacetamide in CCl_4 yield results that may be fitted either to a model of indefinite association characterized by a single equilibrium constant of 2×10^{-3} mol^{-1} or to one combining dimer formation with a K_d of 1 mol^{-1} and the addition of monomer to higher polymers with an association constant of 50 mol^{-1}. A centrosymmetric structure was inferred from the low dipole moments[391]. The ring-dimer association of acetamide was inferred from the recent infrared work of Iogansen and coworkers.[392]. The *cis* type of association necessary in ring dimerization is, however, limited to self-association and heterodimer formation with caprolactam, whereas the usual heteroassociation with bases involves the *trans* hydrogen (see Section IV.C.2.a). The problem of preferred dimer or chain association seems to be still open.

From the evidence of isopiestic measurements in benzene, a cyclic trimer structure for trichloroacetamide has been postulated in addition to the dimeric one[384]. In this case $-\Delta H^0$ for adding a third molecule to the dimer is larger than for dimerization [$-\Delta H_d{}^0 = 7.1$, $-\Delta H_{23}{}^0 = 3.7$ kcal/mol]. Thermodynamic data for a few primary amides are available mainly from two sources[393,394], but the $-\Delta H^0$ values show an unreasonably large spread between -1.8 kcal/mol (propionamide in $CHCl_3$) and benzamide (-9 kcal/mol in benzene). Very little is known about the association structure of concentrated primary amide solutions or pure liquids. Existence of chain structures has been inferred from ESCA data[395].

The kinetics of H-bonding was studied by ultrasonic attenuation in two examples: 2-pyridone[396] and *N*-methylacetamide[397,398]. The former, a model compound for ring dimerization, was examined both in CCl_4 and dioxane and the behaviour was observed as typical of fast, diffusion-controlled processes ($\sim 10^9$ mol^{-1} s^{-1}) which are highly solvent-sensitive. *N*-methylacetamide was measured in dimethylacetamide. The data are treated in terms of the equlibrium between monomer and polymer.

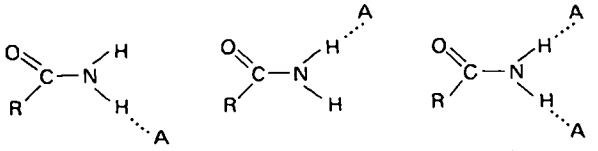
2. *Heteroassociation*

a. Amides as proton donors. The relatively simpler case of secondary amides lends itself to the investigation of the acidic character of the amide NH group. Pullin and Werner[399] have recorded the ν_{NH} shifts of *N*-methylbenzamide in a series of weakly basic solvents, amongst which are some tertiary amides along with ν_{NH} shifts of indole, pyrrole and some amines. The also determined the free-energy changes. This allowed the establishment of a product rule for frequency shifts which expresses the $\Delta\nu$ as the product of two quantities characterizing the solvent sensitivity of the donor and the acceptor, respectively. A product rule dividing the ΔG^0 into contributions from the donor and the acceptor is also given. These contributions represent a useful characteristic which ranges the NH group of

N-methylacetamide between pyrrole and diphenylamine. Clearly, the product rules are applicable only to rather closely related groups. Le Gall and coworkers[400] have determined the association constants of diacetamide, succinimide, maleimide and phthalimide with a series of proton acceptors of increasing basicity. The results indicate that the donating propensity of these imides is very similar. Moreover, these data are compared with corresponding ones for several other types of NH and OH donors. Imides rank as better donors than alcohols but weaker than phenols. Self-association constants of diacetamide and maleimide are also given.

Infrared spectra in the ν_{NH} region of complexes of caprolactam with acceptors of varying strength up to pyridine have been investigated by Dementjeva and coworkers[401]. The main point is the explanation of the appearance of additional absorption maxima in terms of Fermi resonance.

The investigations of H-bonding with primary amides as proton donors are primarily concerned with the structure of complexes. With two hydrogens available 1 : 1 complexes may be formed with either the *cis* or the *trans* hydrogen involved (**7a** and **7b**) as well as 1 : 2 complexes (**7c**). Most of the work is done by i.r.



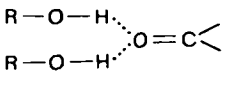
(7a) (7b) (7c)

spectroscopy and difficulties in the interpretation of spectra are due to the vibrational coupling of both NH oscillators and to the presence of the $2\delta_{NH_2}$ overtone near 3100 cm^{-1} engaged in Fermi resonance with ν_{NH_2}. The coupling gives rise to two bands (ν_s and ν_{as}), which are separated in the free NH_2 group by about 118 cm^{-1}. A smaller part ($\sim$ 30 cm^{-1}) of this is due to the inequivalence of the NH group with respect to the proximity of the C=O group. If one group is engaged in H-bonding the coupling, and thus the splitting, are changed and, through shifting, the extent of the Fermi resonance is also influenced. This means that neither the shift nor the intensity are any more directly related to the strength of bonding. These difficulties can be partly overcome by measuring the NH or ND frequencies of the partly deuterated amides (NHD) where the vibrational coupling is removed. Combining these data with a careful analysis of free NH group frequencies of 1 : 1 complexes it was established for several aliphatic secondary amides[402,392] that the *trans* complexes prevail although the *cis* complexes are slightly more strongly H-bonded. The relative strength of the *cis* and *trans* complexes as estimated from ν_{NHD} frequencies corresponds to what was also observed in self-association[402,392].

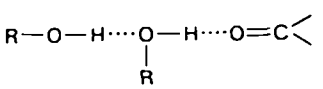
The 1 : 2 complexes appear only with a large excess of the acceptor (e.g. amide 10^{-2} M in $CHCl_3$, acceptor 10 M[402]). An estimate of the enthalpies from the intensity of the ν_{NH_2} bands shows that the bonding of the second acceptor molecule is weaker than that of the first[392].

In acetamides with α-substituted proton acceptors (halogens, alkoxyl) the *trans* hydrogen forms weak intramolecular H-bonds[403]. In this case *cis* intermolecular H-bonding is favoured. Thermodynamic quantities of H-bonding of acetamide, and chloroacetamides with triethylamine in $CHCl_3$, have been determined and the $-\Delta H^0$ values increase from acetamide (1.9 kcal/mol) to trichloroacetamide (3.0 kcal/mol). The values appear somewhat low in view of the strong acceptor triethylamine.

b. Amides as proton acceptors. There are in principle two acceptor sites in amides but there is ample experimental evidence besides the theoretical calculation[331] in favour of the oxygen[404]. Usually the site of protonation is assumed to be identical with that of H-bond accepting on the premise that the H-bond is predominantly of electrostatic character. The latest evidence for the protonation site stems from ^{14}N core-level electron spectroscopy[405]. 1 : 1 and 1 : 2 complexes with proton donors exist and with the latter type complexes the problem arises as to whether the second donor is bonded directly to the amide carbonyl or to the first bonded donor molecule. Infrared spectroscopic evidence has been given for dimethylacetamide to accept two alcohol or phenol molecules to the carbonyl (**8a**)[406] and similarly γ-butyrolactone to accept two molecules of *o*-cresol[407]. The free energy of bonding has also been determined both for the 1 : 1 and 1 : 2 complexes, $-\Delta G^0$ for the latter being slightly less than half that for the 1 : 1 complex. This seems to be at variance with the precision vapour pressure determination of thermodynamic quantities of association of *N,N*-diethyldodecanamide and methanol[408]. The results of this investigation show an increased tendency, expressed both in larger $-\Delta\overline{G^0}$ and $-\Delta\overline{H^0}$, to add molecules beyond the first, which indicates a cooperative effect. Such an effect is possible only if the second and further molecules of methanol add chainwise (**8b**) to the first. The cooperative effect involved in this type of association is well known in water and alcohols[409].



(8a)



(8b)

From the chemical point of view it is interesting to have some amide C=O group characteristics relative to other types of carbonyls, concerning its propensity both for H-bonding and for protonation, as well as its susceptibility to the influence of substituents. Quantum-chemical calculations predict the amide carbonyl to be a considerably better proton acceptor than the aldehydes[331]. Experimental comparisons are possible on the pK_{HB} scale (pK_{HB} = log of H-bond formation constant between the reference acid *p*-fluorophenol and the proton acceptor). The published data include 7 amides amongst more than 100 other acceptors[319]. In fact, the amide carbonyl not only ranks highest amongst other carbonyl compounds, but is also strong in relation to other types of acceptor. Its accepting propensity is influenced by substituents and correlations of pK_{HB} with σ_I and σ_R^+ substituent constants were established[319]. Enthalpies of H-bonding of tertiary amides with phenol were earlier correlated with σ^+ substituent constants[410], but the log K_a did not correlate linearly, probably because of the unaccounted for steric effects.

Effects of substituents in the series of 16 *N,N*-dimethylbenzamides and cinnamamides on the carbonyl group as proton acceptor have been investigated by Spaargaren and coworkers[411]. Both the amide $\nu_{C=O}$ frequency changes and the ν_{OH} of phenol were measured and correlated with the substituent constants of Swain and Lupton[412]. The spectral parameters of H-bonding were also correlated with electronic charges and bond orders as calculated by Hückel's method. Linear relationships between proton magnetic resonance shifts, $-\Delta H^0$, and log K_{ass} values for the association of $CDCl_3$ with several tertiary amides were established. The $-\Delta H^0$ values correlate with the σ substituent constants by the same straight line as sulphoxides[413].

Association constants of 20 phenols of different acidity with acetamide, *N*-methylacetamide and dimethylacetamide have been determined by Dorval and Zeegers-Huyskens[414,415] and correlated with Hammett's σ constants. The ρ values of the three groups of amide complexes are different and their order primary > secondary > tertiary corresponds to the order of their pK_A values. A linear relationship between the pK_{HB} values and the aqueous pK_A values exists for the large family of carbonyl compounds but only formamide has been included[319]. Adelman[415a] has characterized the carbonyl basicity in a series of 15 *N,N*-dialkylamides by potentiometric titration, $\nu_{C=O}$ shifts in chloroform, ν_{OH} shifts of phenol and by complexing with iodine. The results are discussed in terms of σ substituent constants and steric requirements of the bonding acids.

Far-infrared spectra of complexes of five phenols with *N,N*-dimethylacetamide and *N*-methylacetamide in benzene solution have also been recorded. Approximate force constants derived from the σ_{OHO} frequencies reflect the strength of H-bonding and the frequencies of both type of complex correlate linearly with the logarithm of the association constants. However, the correlations of the $\nu_{C=O}$ and σ_{OHO} follow different lines for the monomethyl and dimethyl complexes[416].

Several determinations of thermodynamic parameters of H-bonding of phenols and other proton donors to amides as acceptors have been made. Data published prior to 1969 are collected in Reference 417. Some values of $-\Delta H^0$ (in kcal/mol) for *N,N*-dimethylacetamide–phenol association may be quoted to illustrate the reliability of the data: 5.1 (infrared[418]), 6.84 (ultraviolet[419]), 5.1 (n.m.r.[386]). The most reliable value seems to be that of Arnett's group[320] obtained by the calorimetric method: 7.36 kcal/mol. This value has been checked against infrared and n.m.r. determinations. Similar high quality data are also given for a few other amides. It appears odd that $-\Delta H^0$ for the HF–dimethylformamide association is nearly the same as for phenols: 7.6 kcal/mol[420].

3. *Amide–water association*

a. Theoretical. H-bonding between amides as peptide bond models and water molecules is of exceptional importance for biophysics. Several quantum-chemical investigations have been made in order to explore the possible sites of bonding, geometries of complexes and degree of association. We shall summarize the results of the *ab initio* calculations which add reliability to the semiempirical approaches[421]. Amide–amide bonding is predicted to be weaker by 1 kcal/mol than amide–water C=O . . . HOH bonding[331]. The amide–amide bonding is stronger than the amide–water NH . . . OH_2 bonding, but the water OH is a better proton donor than the amide NH by 1 kcal/mol. The C=O group is by 2.4 kcal/mol a better bonding site than the amide NH. These results were obtained with a moderately extended basis set (431-G) and differ significantly from those yielded by the small set (STO-3G). With the latter the stability is (amide–amide) > (amide–NH . . . OH_2) > (amide–C=O . . . HOH). Subsequent calculations using larger basis sets confirm those obtained by the 431-G set[422]. The absolute values of energies are likely to be exaggerated, but the relative stabilities should be trusted. It is worth noting that the water OH bonding to the C=O lone pair *cis* to NH is slightly more favourable than to the *trans* pair[331]. Ottersen and Jensen[423] have computed the potential functions for the NH . . . O and CO . . . HOH H-bonds and the force constants of the formamide–water complex. The addition of a second water molecule is an important problem, but has been approached only at the STO-3G level. Johansson and coworkers[331] have calculated

the stabilization energies both by placing the second molecule on different amide sites and on the first water molecule. It has turned out that the second mode of bonding yields additional stabilization which is known from other H-bonded trimers and polymers as the cooperative effect[333]. Hinton and Harpool[332] have in succession added five water molecules to both lone pairs of the carbonyl, both amino hydrogens and the fifth one so as to bond to the first water molecule and the OH group. In this way the cooperative effect could not have appeared.

b. Experimental. Investigations of the infrared spectra in the overtone region of *N*-methylpropionamide–water mixtures[424] indicate that water disrupts the amide–amide bonds which are replaced by C=O . . . HOH H-bonds. From the absorption band areas it appears that in a solution of 0.34 mol fraction of water, in which there are approximately the same number of water protons and amide C=O groups, the amide–water interaction is strong. With further dilution water molecules bond to themselves. Other properties of amide–water solutions such as viscosities[425], excess molar volume and dielectric constants also exhibit singularities, but not at the same mol fractions. However, the dilution curve of the ^{13}C chemical shift of formamide also shows a strong inflexion at about 0.3 mol fraction of water[426]. A possible interpretation is along the theoretically predicted model[331].

Determinations of proton spin-lattice relaxation rates of dimethyl formamide–water systems also show flat maxima of $1/T$ in the range of 40 mol.-%[427]. Some indications as to the formation of complexes of definite stoichiometry were deduced from the dilution curves, but the differentiation between contributions from various relaxation processes are difficult and hence the treatment of data at this stage is not unamibiguous. Measurements of ^{13}C and ^{15}N spin-lattice relaxation times and nuclear Overhauser enhancements of acetamide and *N,N*-dimethylacetamide in a limited range of dilutions with water also suggest that the amide–amide bonds are replaced by amide–water bonds[428]. The study of nicotinamide in water using ^{1}H and ^{13}C magnetic resonance spectroscopy[429] shows that the amide is self-associated at high concentrations but that amide–water bonding takes over on dilution. Self-association by H-bonding in contrast to the possible stacking of the pyridine rings is of importance because nicotinamide is an essential fragment of nucleotide coenzymes. In this study indications were obtained that the *trans* protons exchange more rapidly with water than the *cis* ones.

The most extensive infrared determination of thermodynamic parameters of H-bonding of tertiary amides with water in dilute CCl_4 solutions was made by Henson and Swenson[430]. The $-\Delta H^0$ vary from 3.2 to 4.7 kcal/mol in the series from *N,N*-dimethylformamide to *N,N*-dimethylisovalerylamide, but *N,N*-dimethylbenzamide is outstanding with $\Delta H^0 = 7.57$ kcal/mol. A comparison with other proton donors in H-bonding to amides ranges water between alcohols[431] and phenols[320].

The rather scanty knowledge of amide–water interactions, particularly in the way of dynamics involving H-bonding, is certainly not due to the lack of interest, but to experimental difficulties. The developments in n.m.r. techniques as well as in the combination of quantum-chemical and statistical-mechanical methods should bring significant progress in the future.

D. H-Bonding and Internal Rotation

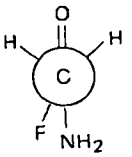
The influence of H-bonding on the barrier for rotation about the C–N bond is important with respect to the conformational behaviour of peptide links. Theoret-

ically, proton accepting by either the carbonyl oxygen or the nitrogen atoms should increase the double-bond character of C—N and hence the barrier[330], whereas proton donation by NH should lower it. Some relevant results prior to 1969 are given in a review[432]. The results of Kamei[433] are also in agreement with this. He has observed the changes in the decoupled NH_2 magnetic resonance shifts of formamide in water, acetone and dioxane as a function of temperature. The calculated barrier for the formamide–water system was higher than for neat formamide whereas it was lower for the other two solvents. This is also additional evidence that water–amide C=O . . HOH bonding is stronger than amide–amide bonding. The trends in the $^{13}C-^{15}N$ coupling constant in formamide diluted by water are similarly interpreted[426]. The activation energy for the rotation about the amide C—N in *N*-methyl-*N*-benzyl-*o*-chlorobenzamide is increased by ~2 kcal/mol by H-bonding with phenol as demonstrated by the n.m.r. investigation of Siddall, Pye and Stewart[434]. However, the barriers for acetamide in water, dimethylsulphoxide and acetone determined by the n.m.r. method[435] are at variance with the results obtained with formamide[433], the lowest barrier being found in water. However, the error given in this work is larger than in Kamei's[433] and the differences between the solvents are within the error limits.

Williamson and Roberts[436] have investigated conformational equilibria of 5 to 9 and 13-membered lactams in neutral, proton-donating and proton-accepting solvents by following the ^{15}N and ^{13}N chemical shifts. $CDCl_3$ shows strong influence but the rationalization of solvent effects is difficult. It is appropriate to mention here that tertiary amides undergo appreciable self-association and association with other carbonyl compounds by dipole–dipole interaction. This kind of association also influences the rotational barriers[437,438].

E. Intramolecular H-Bonding in Amides

H-bonding between an amide NH and a proton-accepting substituent in the α-position is of interest because of the influence of such bonding on the conformation, which is much larger than the indirect influence of intermolecular bonding. The most precise information about the conformation of the simplest example, 2-fluoroacetamide (**9**), is available from microwave spectroscopy[439]. The conform-



(9)

ation is dominant in the gas phase as well as in the solid[440] and in dilute CCl_4 solution[441]. The N . . . F distance is by 0.2 Å shorter than the sums of the NH and F van der Waals' radii, but the proton is not on the N . . . F line. Extensive series of substituted secondary amides have been investigated by Nyquist[442,443] and Jones[444] and some primary amides by Bessonova and Ginzburg[445]. The α-substituents were halogens, methoxy and phenoxy groups. Intramolecular H-bonding to these groups is demonstrated by a slight lowering of the ν_{NH} in very dilute CCl_4 solution and an increase of intensity. Although the thermodynamic parameters of association were not derived, relative ν_{NH} intensity considerations show that the tendency to self-association, and particularly the formation of higher

aggregates is reduced by intramolecular bonding. With very bulky *N*-substituents the intramolecular bonding is dominant, even in the liquid state[444]. Such an example is *N*-(*t*-butyl)methoxyacetamide. Keto groups in appropriate positions, such as in pyruvamides[446] and acetoacetanilides[447], are also strong acceptors. Proton acceptors in the *ortho* position and the *N*-substituents of benzamides may compete for the intramolecular H-bond[448].

V. H-BONDING IN THIO CARBOXYLIC ACIDS AND THIO AMIDES

A. Thio Acids

H-bonding studies of the thiol form, which is the dominant tautomer, have been done mainly on thioacetic and thiobenzoic acids. The H-bond in these acids is much weaker than in carboxylic acids since no self-association of thioacetic acid is detectable in the gas phase[449]. However, in CCl_4 and benzene solutions the concentration dependence of the infrared SH stretching band of thioacetic and thiobenzoic acids, as well as of their ^1H magnetic resonance signals, indicates association[450–454]. Possibly both the open and the closed dimers are in equilibrium with monomeric acid molecules. Open dimers are predicted to be more stable by CNDO/2 calculations[455], but experimental evidence, though not quite conclusively, indicates the cyclic thiol dimers to be more stable[456]. Enthalpies of dimerization in CCl_4 have been determined[457,458] for some thiobenzoic acids and $-\Delta H^0$ per H-bond varies between 2.8 and 3.3 kcal/mol. The $-\Delta H^0$ values correlate with Hammett's σ substituent constants and the value of ρ suggests that the substituent's influence on the strength of H-bonding is exercised primarily through the thiol group. H-bonding in trifluorothiolacetic acid is much weaker than in the other two examples since infrared spectra indicate bonding effects only in the solid acid[459]. Similarly, the ν_{SH} band of liquid thioformic acid at room temperature seems not to be influenced by any H-bonding[460], but the broadening of the SH n.m.r. signal at low temperature in CS_2 indicates that H-bonds are formed[454]. Indications of OH . . . S bonding of the thion form of trichlorothioacetic acid have been reported[461].

B. Thio Amides

Most of the investigations of H-bonding in thio amides seem to have been motivated by differences in the bond character of the amide group induced by sulphur. Comparison[462] between thermodynamic parameters of dimerization in CCl_4 of thiobutyrolactam, thiovalerolactam and thiocaprolactam, and the corresponding lactams shows that the $-\Delta H_d{}^0$ of the former are definitely smaller and so are the $-\Delta S_d{}^0$ values. Hence the $-\Delta G^0$ values of thio lactams and lactams are comparable.

It is interesting to consider separately the proton donating ability of the NH group and the acceptor characteristic of >C=O and >C=S, respectively. The association constants of some imides and the corresponding thio imides with several bases indicate[400] that the NH(C=S) groups are more acidic than NH(C=O) which is in agreement with the larger positive charge on the former obtained by MO calculations[463]. The C=S group of *N,N*-dimethylthioacetamide appears to be an acceptor slightly inferior to the C=O group of the *N,N*-dimethylacetamide as demonstrated by the ΔH^0 values of complexation with fluorinated alcohols[464].

However, the $\Delta\nu_{OH}$ of these alcohols bonded to either amide are hardly any different. This base pair together with several other sulphur–oxygen analogous bases were used to discuss the differences between $\Delta\nu_{OH}$ vs $-\Delta H^0$ correlations for oxygen and sulphur bases in terms of different 'hardness' of both elements. The smaller proton-accepting propensity of sulphur in dimethylthioformamide and tetramethylthiourea as compared with the oxygen analogues is also discussed by Reyntjens and Zeegers-Huyskens[465]. $\Delta\nu_{OH}$ and association constants with phenols are the experimental basis of this discussion and the data as well as the main ideas are in agreement with the earlier work of Gramstad and Sandström[466].

Whereas the frequency differences between the *cis* and *trans* NHD stretchings in primary amides complexed to proton acceptors allowed conclusions as to the structure of these complexes in solution (Section IV.C.2.a), such differences are not apparent with thioacetamide[467]. However *N*-monosubstituted thio amides do exhibit differences due to *cis–trans* isomerism both in the ν_{NH} frequencies and in chemical shifts. The secondary *cis* thio amides form cyclic dimers and also polymers in more concentrated solutions, whereas *trans* thio amides associate into chains[468,469]. The differences in the $\Delta\nu_{OH}$ of thioacetamide bonded to weak and strong acceptors are surprisingly small[467] ($\Delta\nu$ acetonitrile $-\Delta\nu$ pyridine $= 34\ cm^{-1}$), which seems to be due to Fermi resonance between ν_{NH} and $2\delta_{NH}$. Infrared spectral investigations of Walter and Vinkler[470] on several thio amides in polar and non-polar solvents indicate the formation of both 1 : 1 and 1 : 2 complexes.

Intramolecular H-bonds between the amide NH of phenylthioacetamide[471,478] and the aromatic ring are formed, and similarly in 2-aminobenzamides as well as in *o*-substituted thio anilides[472]. Intramolecular H-bonding creates preference for the *trans* isomers, as observed in i.r. and n.m.r. spectra[468,472].

Heterocyclic thio amides such as 2-thiapyridone and mercaptobenzothiazole give rise to particular interest because of their ν_{NH} bands which are very broad, display even more subsidiary maxima than the carboxylic acid dimers and the band centres are lower than with ordinary thio amides[473]. For instance the strongest peak of 2-thiapyridone is $\sim 2990\ cm^{-1}$, whereas normal thio amides[474] absorb near $3160\ cm^{-1}$. Cooperative proton-transfer effects connected with tautomerism have been involved in order to explain the unusual features in the infrared spectra of the heterocyclic thio amides and in particular the striking reduction of band width in the ND analogues[473]. However, the NH . . . S distance in mercaptobenzothiazole[475] is 3.35 Å and in 2-thiapyridone[476] it is 3.26 Å. Both associate to centrosymmetric dimers in the solids. The $R_{N\ldots S}$ are thus not essentially shorter than in thioacetamide[477] or 4-pyridinethioamide[478] where interdimer H-bonding appears to be the dominant association pattern in these solid primary thio amides as in the amide series. series.

Dimerization constants of thiazolidine-2-thione, mercaptobenzothiazole, and 4-methylthiazoline-2-thione have been determined[479] in CCl_4 using the infrared technique. The constants (at 25°C) increase in the order of compounds as above from 88 to 570 and 5540 mol^{-1} and this order also corresponds to the decreasing ν_{NH} frequencies. The band centre of the last compound is about $2880\ cm^{-1}$.

The $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ electronic absorption bands of the thione group are in the region above 200 mμ and display pronounced H-bonding effects. The spectra of thioacetamide and its *N*-methyl derivatives in some protic solvents have been recorded by Janssen[480] and the effects of H-bonding on the electronic spectra of three heterocyclic thio amides have been more systematically explored by Ellis and Griffiths[481].

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER 7

The synthesis of carboxylic acids and esters and their derivatives

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I. INTRODUCTION

Since other volumes in the series, *The Chemistry of Functional Groups*, do not presently contain chapters devoted exclusively to discussions of standard methods for the preparation of carboxylic acids and esters, our major goal in writing this chapter has been to systematically present the most widely applicable procedures for synthesizing these two classes of compounds. We have also included discussions of recent developments in the synthesis of anhydrides, acyl halides, amides and imides.

The primary literature surveyed for this chapter covers mainly the years 1967 through 1975, with some citations from the 1976 literature. Synthetic methods which have been reviewed elsewhere are given brief treatment, and the reader is provided with references to these sources.

We have attempted to include as representative examples of synthetic methods, procedures which are well tested and clearly described. Almost certainly some methods will be overlooked or judged to be of insufficient generality to warrant inclusion. We hope, however, that such instances will be few and that this chapter may be useful to the international community of synthetic organic chemists.

II. SYNTHESIS OF CARBOXYLIC ACIDS

Standard methods for the synthesis of carboxylic acids have been reviewed in the texts by Buehler and Pearson[1] and by Sandler and Karo[2]. More specific reviews published since 1950 have dealt with the synthesis of fatty acids[3-8], dicarboxylic acids[9-12] and polycarboxylic acids[13,14].

A. Acids by Hydrolysis Reactions

Numerous synthetic procedures initially afford carboxylic acid derivatives, which can subsequently be hydrolysed, or cleaved in a fashion analogous to hydrolysis, to give free acids. Esters and nitriles resulting from active-hydrogen condensations and nucleophilic substitutions are encountered most frequently in this context. In addition to the usual acid derivatives, certain other functional groups such as di- and trihalomethyl can be converted into acids by hydrolytic methods.

1. Hydrolysis of esters

Hydrolysis of esters can be carried out in the presence of various acidic or basic reagents. Acidic hydrolysis (equation 1) is a catalytic process in which the products and reactants reach equilibrium concentrations unless the reaction is forced toward

$$R^1COOR^2 + H_2O \overset{H^+}{\rightleftharpoons} R^1COOH + R^2OH \quad (1)$$

the desired acid. In most instances of synthetically useful acidic hydrolyses, water is provided in sufficient excess to favour production of the carboxylic acid and alcohol. Alkaline cleavage of esters (equation 2) is not a catalytic process, since a molar equivalent of hydroxide ion is consumed for each equivalent of ester converted to carboxylate salt.

$$R^1COOR^2 + OH^- \longrightarrow R^1COO^- + R^2OH \quad (2)$$

Because of its essential irreversibility, saponification by aqueous or alcoholic alkali metal hydroxides is the most widely used method for the hydrolytic cleavage of unhindered esters which are not otherwise sensitive to hydroxide ion. Numerous well-tested examples of saponification reactions may be found in the collected volumes of *Organic Syntheses*[15]. Typical of such a process is the hydrolysis of *trans*-methyl 2-methyl-2-dodecenoate to *trans*-2-methyl dodecenoic acid (equation 3)[16] and the saponification of dimethyl hendecanoate to methyl hydrogen

$$C_9H_{19}CH{=}CMeCOOMe \xrightarrow[\text{aq. EtOH}]{KOH} C_6H_{19}CH{=}CMeCOOH \quad (3)$$

hendecanedioate (equation 4)[17]. The latter procedure affords the monoester

$$MeOOC(CH_2)_9COOMe \xrightarrow[MeOH]{Ba(OH)_2} MeOOC(CH_2)_9COOH \quad (4)$$

because the barium salt of this product precipitates from the reaction solution. The hydrolysis of low molecular weight esters by aqueous sodium hydroxide is aided by addition of catalytic amounts of quaternary ammonium salts as phase-transfer catalysts[18].

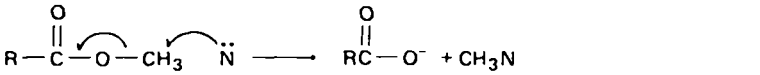
Acidic hydrolysis of esters is often accomplished by refluxing the ester with aqueous hydrochloric acid, alone[19] or in the presence of a suitable cosolvent such as dioxane[20]. Acid-catalysed cleavage becomes the method of choice for esters which contain another functionality which is sensitive to aqueous alkali. For example, methyl 2,3-dibromopropionate is smoothly converted into 2,3-dibromopropionic acid by aqueous hydrobromic acid[21]. However, in some instances it is desirable to effect concomitant saponification and elimination of

base-sensitive groups, e.g. in the preparation of stearolic acid from methyl 9,10-dibromostearate[22] and in the synthesis of muconic acid from α,δ-dibromoadipate[23].

Two major problems arise in the synthesis of carboxylic acids from esters. These are: (*i*) the reluctance of certain esters to undergo either acidic or basic hydrolysis because of steric hindrance, and (*ii*) the sensitivity of various functionally substituted esters to both aqueous acid and base.

Hydrolytic cleavage of sterically hindered esters can be accomplished in several ways. For example, mesitoic esters are hydrolysed by dissolution in 100% sulphuric acid followed by quenching in cold water[24]. More recently, it has been reported that alkyl mesitoates can be saponified in excellent yields by the potassium hydroxide complex of the macrocyclic ether, dicyclohexyl-18-crown-6 in refluxing benzene or toluene[25].

A useful approach to the cleavage of hindered esters involves displacement of carboxylate ion from the alkyl group of the ester by a suitable nucleophilic reagent (equation 5). As would be expected for a bimolecular nucleophilic displacement,

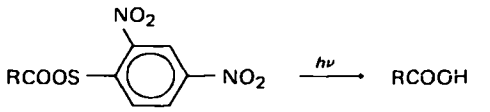


(5)

methyl esters participate most readily in such reactions. Lithium iodide in pyridine, 2,6-lutidine or 2,4,6-collidine[26] and potassium *t*-butoxide in dimethyl sulphoxide (DMSO)[27] appear to be the first reagents recognized for their generality in such reactions. Later modifications of these procedures include the use of lithium iodide in dimethylformamide (DMF)[28,29], lithium iodide–sodium cyanide in DMF[30] and dimsyl sodium in DMSO[31,32]. Lithium *n*-propyl mercaptide in hexamethyphosphoramide (HMPA)[33], and sodium ethylmercaptide in DMF[34] readily cleave hindered esters such as methyl triisopropylacetate and methyl *O*-methylpodarpate. Other sulphur nucleophiles such as trithiocarbonate[35] and sodium ethanedithioate[36] in acetonitrile have been used to effect the cleavage of 2-haloethyl esters. The utility of these reagents with hindered esters has not yet been established. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) has been found to act as an effective non-ionic nucleophile for the cleavage of hindered esters[37]. This reagent has also been used to cleave toluene-*p*-sulphonylethyl esters, presumably by β-elimination of carboxylate ion[38]. Boron trichloride in methylene chloride is an effective reagent for converting hindered esters to acids, although its mechanism of action is obviously not analogous to that of nucleophilic reagents[39].

The problems associated with the synthesis of carboxylic acids from esters containing other hydrolytically unstable functions may be circumvented by employing esters with *O*-alkyl groups which are susceptible to cleavage under anhydrous conditions. Many of the procedures discussed above for hindered esters are satisfactory, provided methyl esters are employed. Classical methods for anhydrous decomposition of esters to acids involves the use of *t*-butyl esters, which can be cleaved thermally[40] or in the presence of anhydrous acid[41,42]. Tetrahydropyranyl esters are likewise sensitive to anhydrous acid[43–46]. Benzyl esters undergo hydrogenolysis to form toluene and carboxylic acids[47–49]. Phenacyl esters can also be cleaved by catalytic hydrogenolysis[50] and by sodium thiophenoxide in anhydrous DMF[50]. Benzyl esters afford acids on treatment with trifluoroacetic acid[51] or formic acid[49].

Photolysis of 2,4-dinitrobenzenesulphenyl esters provides a route to carboxylic acids under mild, anhydrous conditions[52] (equation 6). 2,2′-Dinitrodiphenylmethyl



(6)

and *o*-nitrobenzyl esters react similarly upon near ultraviolet irradiation to afford carboxylic acids in excellent yields[53].

Lactones can be hydrolysed to afford hydroxy[54] and halo acids[55] using reaction conditions similar to those employed for acyclic ester hydrolysis.

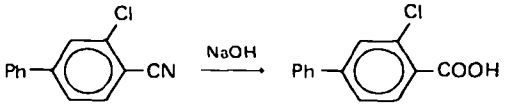
2. *Hydrolysis of nitriles*

The ease with which a cyano group can be introduced into various molecules by nucleophilic displacement, addition to carbonyl groups of aldehydes and ketones, hydrocyanation of α,β-unsaturated carbonyl compounds, and even direct aromatic substitution, makes the nitrile function an extremely useful precursor to carboxylic acids.

Hydrolyses of nitriles can be carried out under basic or acidic conditions (equation 7). The former appear to be employed more frequently than the latter.

$$RCN + H_2O \xrightarrow[OH^-]{H^+ \text{ or}} RCOOH \tag{7}$$

Alkaline hydrolyses are promoted by ethylene glycol[56], diethylene glycol[57] and glycerol[58]. Typical examples of base-promoted hydrolyses of nitriles appear in the syntheses of 3-chlorobiphenyl-4-carboxylic acid[59] (equation 8) and 3-*t*-butylpentanedioic acid[60] (equation 9). The syntheses of cyclopropane carboxylic acid[61] from γ-chlorobutyronitrile and methylsuccinic acid[62] from ethyl crotonate are illustrative of reactions which employ alkaline hydrolysis of a nitrile preceeded by ring closure and hydrocyanation, respectively.



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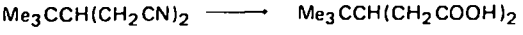
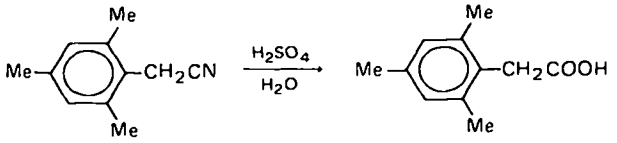


(9)

Acidic hydrolyses are typified by the synthesis of mesitylacetic acid from mesitylacetonitrile[63] (equation 10) and by the preparation of *o*-toluic acid from *o*-toluonitrile[64]. Aqueous hydrochloric[65,66] and hydriodic[67] acids are useful reagents for nitrile hydrolysis.

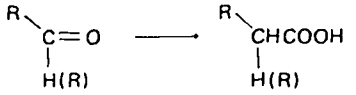


(10)

Sterically hindered nitriles can usually be hydrolysed efficiently by alkali hydroxides in ethylene glycol[56] or diethylene glycol[57]. However, in some instances it may be advantageous to first convert the nitrile to a primary amide by means of a suitable reagent such as concentrated sulphuric acid[68] or polyphosphoric acids[69]

and then hydrolyse the amide with nitrous acid. The combined action of sulphuric acid and sodium nitrite on nitriles may be satisfactory without necessitating the isolation of the intermediate amide[70].

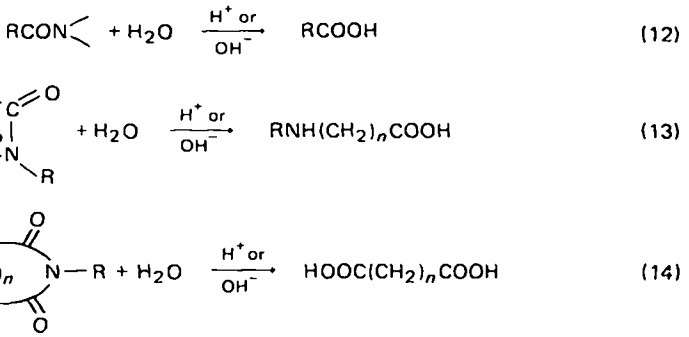
Hydrolysis of the nitrile function plays an important role in the synthesis of α-amino acids (Strecker Synthesis)[71-73] and α-hydroxy acids[73,74] from aldehyde and ketone cyanohydrins (equation 11). Cyanohydrin formation and hydrolysis can also serve as a method for homologation of aldehyde and ketone carbonyl groups to the next higher carboxylic acid[75,76]. A convenient application of this method involves reaction of aromatic aldehydes with glyoxal bisulphite and alkaline cyanide to afford arylacetic acids[77].



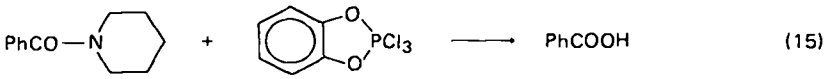
(11)

3. *Hydrolysis of amides*

Primary, secondary and tertiary amides, as well as lactams and imides undergo hydrolysis in the presence of alkali hydroxides or mineral acids in much the same manner as do esters and nitriles. Recently, aqueous sodium peroxide has been used



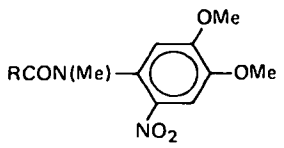
to effect the hydrolysis of amides[78]. Certain amides are also converted to acids by *o*-phenylenedioxyphosphorus trichloride[79] (equation 15).



Hindered amides can be converted to acids by potassium hydroxide in diethylene glycol[80]. Other methods involve the use of nitrous acid[81], or sulphuric acid and sodium nitrite[82], or *n*-butyl nitrite and a mixture of hydrochloric and acetic acids[83]. Hindered secondary amides can be hydrolysed by first converting them into *N*-nitroso derivatives, which then undergo decomposition to afford the acid[84,85]. Nitrosonium fluoroborate[86] in acetonitrile represents an attractive reagent for the hydrolysis of hindered amides under anhydrous conditions.

N-Methyl-*N*-(2-nitro-4,5-dimethoxyphenyl)amides have been found to undergo photolytic cleavage to the respective acids in good yields (equation 16)[87].

Two types of reactions which are analogous to the hydrolysis of amides involve oxidative cleavage of acylhydrazides and hydroxamic acid derivatives. Acylhy-



(16)

drazides afford acids upon treatment with ferric chloride[88], NBS[89], manganese dioxide[90], ceric ammonium nitrate[91], lead tetraacetate[92], sodium hypochlorite[93] and molecular oxygen in the presence of cupric acetate (equation 17)[94]. Hydroxamic acids are cleaved to give carboxylic acids by aqueous periodate (equation 18)[95,96].

$$R^1CONHNHR^2 \xrightarrow{[O]} R^1COOH \tag{17}$$

$$RCH_2CONHOH \xrightarrow{HIO_4} RCOOH \tag{18}$$

4. *Hydrolysis of acyl halides and anhydrides*

Acyl halides and anhydrides can be hydrolysed without the necessity of acidic or basic catalysts (equation 19)[97,98]; however, mineral acids[99], alkali hydroxides[100] and tertiary amines[101] are sometimes used to accelerate the hydrolyses of anhydrides. In general, acyl halides are prepared from the free acid in order to activate the acyl function toward nucleophilic acyl substitution and are therefore seldom employed in hydrolytic preparations of acids.

$$\begin{matrix} RCOCl \\ \text{or} \\ (RCO)_2O \end{matrix} \xrightarrow{H_2O} RCOOH \tag{19}$$

5. *Hydrolysis of trihalides*

A trihalomethyl group serves as a convenient predecessor to the carboxyl function (equation 20). Although the hydrolysis of benzotrichlorides is a

$$RCX_3 + H_2O \xrightarrow[OH^-]{H^+ \text{ or}} RCOOH \tag{20}$$

well-known route to aromatic carboxylic acids, the trihalomethyl group is not so easily introduced into aliphatic molecules as in the aromatic series, where benzylic halogenation of methylated aromatics is readily accomplished. However, telomerization of olefins with carbon tetrachloride affords α,α,α-trichloro-ω-chloroalkanes[102], which then undergo acidic hydrolysis to form ω-chloroacids (equation 21). A frequently encountered method for introduction of a trichloro-

$$Cl(CH_2CH_2)_nCCl_3 \xrightarrow[H_2SO_4]{H_2O} Cl(CH_2CH_2)_nCOOH \tag{21}$$

methyl group into an aliphatic framework involves base-catalysed condensation of aromatic aldehydes with chloroform to afford aryltrichloromethylcarbinols, which can then be hydrolysed by alcoholic potassium hydroxide to give α-alkoxyaryl-

$$ArCH(OH)CCl_3 + KOH \xrightarrow{ROH} ArCH(OR)COOH \quad (22)$$

acetic acids (equation 22)[103-105]. When the condensation and hydrolysis steps are conducted in the presence of aqueous potassium hydroxide[106,107] or under conditions of phase-transfer catalysis[108] α-hydroxy acids are obtained. An interesting synthesis of bicyclo[3.3.0]octane-1-carboxylic acid involves the formation and acid-catalysed hydrolysis of 1-trichloromethylbicyclo[3.3.0]octane[109].

6. *Hydrolysis of dihalides*

Reaction of compounds containing a 1,1-dichlorovinyl group with concentrated sulphuric acid followed by a water quench produces carboxylic acids, often in excellent yields (equation 23)[110]. A reaction sequence which is somewhat related

$$-CH=C\begin{matrix}Cl\\Cl\end{matrix} \xrightarrow[H_2O]{H_2SO_4} -CH_2COOH \quad (23)$$

to the above process, but considerably milder, involves reaction of appropriate carbonium ion precursors, such as secondary or tertiary alcohols, esters of tertiary alcohols or olefins, with 1,1-dichloroethylene (vinylidene chloride) in the presence of concentrated sulphuric acid or sulphuric acid and boron trifluoride. Hydrolysis of the reaction mixture affords the carboxylic acid with two more carbons than the intermediate carbonium ion. The general features of this type of reaction are shown in equation (24). A comprehensive review of the reaction is available[111]. A recent report describes its intramolecular application[112].

$$R^2-\overset{R^1}{\underset{R^3}{C^+}} + CH_2=CCl_2 \longrightarrow R^2-\overset{R^1}{\underset{R^3}{C}}-CH_2\overset{+}{C}Cl_2 \xrightarrow{H_2O} R^2-\overset{R^1}{\underset{R^3}{C}}-CH_2COOH \quad (24)$$

B. Acids by Condensation Reactions

The syntheses described in this section involve active-hydrogen reactions in which carbanions are key intermediates.

1. *Perkin reaction*

This reaction involves condensation of an aryl aldehyde with acetic anhydride or an α-alkylacetic anhydride in the presence of a base such as the carboxylate salt corresponding to the anhydride or a tertiary amine (equation 25). Although the

$$ArCHO + (RCH_2CO)_2O \xrightarrow[\text{or } R_3N]{RCH_2COONa} ArCH=CRCOOH \quad (25)$$

Perkin reaction is probably the most widely used method for the synthesis of cinnamic acids, aliphatic aldehydes containing α-hydrogens do not react satisfactorily. For a more detailed discussion of the scope and limitations of this reaction, the reader is referred to a somewhat dated review[113] and an excellent discussion of the mechanism[114].

2. Doebner reaction

Malonic acids serve as the active-hydrogen components in this reaction, which is a modification of the Knoevenagel reaction (see Section III.B.1) using pyridine as the reaction solvent (equation 26). The rather mild conditions associated with the

$$RCHO + CH_2(COOH)_2 \xrightarrow{\text{pyridine}} RCH{=}CHCOOH + CO_2 \qquad (26)$$

Doebner reaction permit the use of aliphatic aldehydes, which polymerize rapidly under the more stringent conditions of the Perkin reaction. Thus, this reaction represents a fairly general method for the synthesis of both β-aryl- and β-alkyl α,β-unsaturated acids. Several reviews of the Doebner reaction have been published[114–116].

3. Stobbe condensation

The scope, limitations, and mechanism of this reaction have been reviewed[114,117,118]. The Stobbe reaction involves base-catalysed condensation of diethyl succinate with ketones or aldehydes to form the monoethyl esters of α-alkylidene- or α-aralkylidenesuccinic acids (equation 27). The most satisfactory

$$RCOR(H) + \begin{matrix}CH_2COOC_2H_5\\ |\\ CH_2COOC_2H_5\end{matrix} \xrightarrow{\text{base}} \begin{matrix}RC{=}C\\ |\\ R(H)\end{matrix}\begin{matrix}\diagup COOC_2H_5\\ \diagdown CH_2COOH\end{matrix} \qquad (27)$$

bases for this reaction appear to be potassium *t*-butoxide[119] or sodium hydride[118]. The initially formed alkylidene or aralkylidine ethyl hydrogen succinates can be converted into other acid derivatives such as β,γ-unsaturated acids, γ-butyrolactones and γ-keto acids[114,118,120].

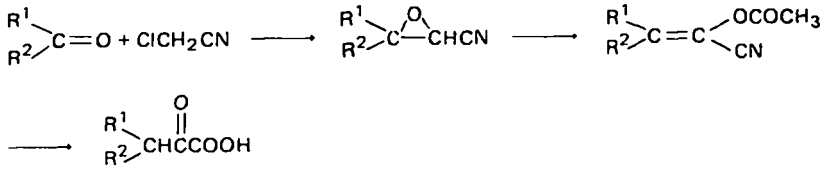
4. Darzens condensation

In its most general form, the Darzens reaction[121,122] involves base-catalysed condensation of α-halo esters with ketones or aromatic aldehydes in the presence of strong bases such as alkali metal alcoholates or amides (equation 28). The resulting

$$RCOR(H) + XCH_2COOEt \xrightarrow{\text{base}} \begin{matrix}RC\diagup O \diagdown CHCOOEt\\ |\\ R(H)\end{matrix} \qquad (28)$$

α,β-epoxy esters (glycidic esters) can be hydrolysed to glycidic acids, which undergo facile decarboxylation to form aldehydes or ketones, depending upon the nature of the α-halo ester employed as the active-hydrogen component. Although the Darzens condensation is not a widely used method for acid synthesis, the aldehydic product resulting from the decarboxylation step can be oxidized to a carboxylic acid as shown in equation (29)[123]. In a recently reported sequence of reactions (equation 30) similar to the classical Darzens condensation, chloroacetonitrile has been condensed with ketones to afford α,β-epoxynitriles, which undergo ring-opening

$$\begin{matrix}R\\ \diagdown\\ C{=}O\\ \diagup\\ R(H)\end{matrix} \xrightarrow[2.\ \text{oxidation}]{1.\ \text{Darzens}} \begin{matrix}R\\ \diagdown\\ CHCOOH\\ \diagup\\ R(H)\end{matrix} \qquad (29)$$



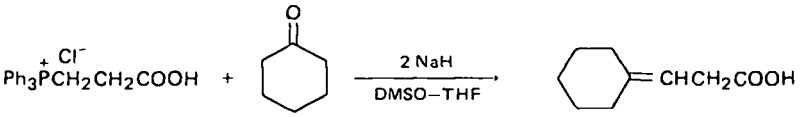
(30)

and elimination upon treatment with hydrogen chloride, acetic anhydride and finally triethylamine, to afford α-cyano vinyl acetates. Acidic or basic hydrolysis of these compounds produces α-keto acids[124].

5. *Wittig-type reactions*

Applications of Wittig-type reactions to the synthesis of free carboxylic acids are encountered much less frequently than those in which esters are the final products. In view of this, the reactions discussed in this section are limited to those in which carboxylic acids are produced directly. Additional examples of the use of Wittig-type reactions for the preparation of esters are discussed in Section III.B.3. A comprehensive review of the Wittig reaction in the synthesis of unsaturated acids and esters has appeared in another volume of this series published in 1969[125]. A recent review of organic phosphonate carbanions as synthetic intermediates includes numerous examples of ester preparations[126].

The most general approach to Wittig-type syntheses of unsaturated acids involves the use of alkylidene phosphoranes containing a free carboxyl group. This procedure is illustrated by the preparation of β-cyclohexylidenepropionic acid (equation 31)[127]. Similar reactions employing other carboxyalkylidenephosphoranes have been used to prepare a variety of unsaturated acids (equation 32)[128–130].



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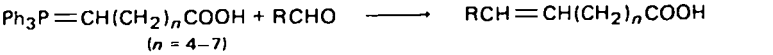
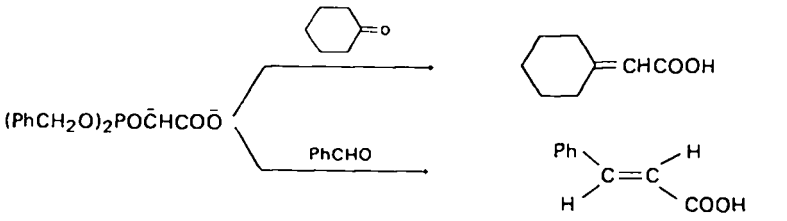


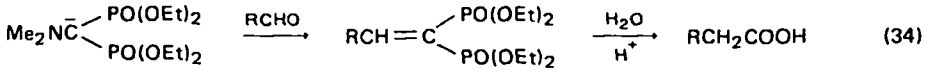
(32)

Carboxyalkyl phosphonates can also be used in the direct synthesis of free carboxylic acids. Thus, the dianion prepared from α-dibenzylphosphonoacetic acid has been employed in the synthesis of several α,β-unsaturated acids (equation 33)[131]. On the basis of these preliminary experiments it would appear that dianions derived from other carboxyalkyl phosphonates could serve as useful intermediates for the synthesis of a variety of unsaturated acids.



(33)

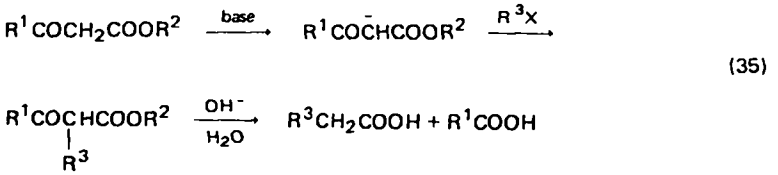
In a novel application of a Wittig-type reaction to the synthesis of carboxylic acids, the carbanion derived from tetraethyl dimethylaminoethylenediphosphonate has been allowed to react with aldehydes to form diethyl 1-dimethylaminoalkenylphosphonates, which can be hydrolysed to α-substituted acetic acids (equation 34)[132].



(34)

6. *Acetoacetic ester synthesis*

The synthesis of carboxylic acids from acetoacetic ester and other β-keto esters involves formation and alkylation of the β-keto ester carbanion, followed by hydrolytic cleavage of the acyl and ester functions of the resulting alkylated β-keto ester (equation 35)[133]. The competing formation of ketonic products resulting

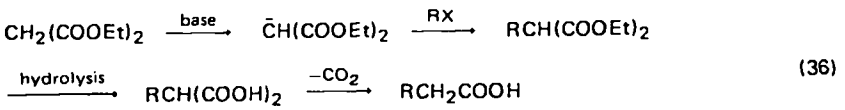


(35)

from decarboxylation of β-keto acids and the presence of two acidic components in the final reaction mixture places this synthesis among the least desirable of active-hydrogen condensations leading to carboxylic acids. However, under certain conditions, the acyl group of α-alkylated β-keto esters can be cleaved without accompanying ester hydrolysis to form α-alkyl acetates, which are isolated and hydrolysed to give α-alkylacetic acids. Such procedures are discussed in Section III.B.5.

7. *Malonic ester synthesis*

This classical method of acid synthesis involves formation and alkylation of the carbanion of malonic esters, followed by hydrolysis and decarboxylation (equation 36). The versatility of the malonic ester synthesis has been demonstrated by its



(36)

application to the preparation of α-substituted acetic acids[134,135], α,α-disubstituted acetic acids[135], dicarboxylic acids[136], cycloalkane carboxylic acids[137], γ-keto acids[138], α-halo acids[139] and α-amino acids[139-144]. Several excellent discussions of the synthetic utility of malonic esters are available[145,146]. Recently[147], diethyl malonate has been shown to undergo alkylation with Δ^1-olefins in the presence of manganese(III) or cobalt(III) acetates to afford 2-alkenylmalonates, which can be hydrolysed to γ,δ-unsaturated acids or cyclized to γ-lactones.

8. *From dianions (α-anions) of carboxylic acids*

A simple, yet elegant alternative to the malonic ester synthesis involves treatment of a carboxylic acid with two molecular equivalents of strong base to produce a dianion intermediate resulting from abstraction of both the carboxyl proton and an α-hydrogen. These dianions react regiospecifically at the α-anion site with electrophilic reagents to form elaborated analogues of the parent acid without requiring ester hydrolysis and decarboxylation.

The α-anion approach was first successfully utilized with phenylacetic acid, which was converted to the dianion by means of potassium or sodium amide in liquid ammonia (equation 37)[148-150]. Alkylations afforded α-substituted phenyl-

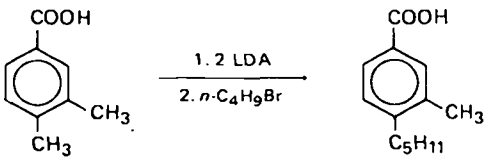
$$PhCH_2COOH \xrightarrow[\text{liq. } NH_3]{2\,KNH_2} PhCHCOO^{=} \xrightarrow{RX} PhCHRCOOH \qquad (37)$$

acetic acids in good yields. Similarly, Ivanov-type[151,152] reagents of arylacetic acids can be prepared by reaction of the acid or acid salt with an alkyl Grignard reagent such as isopropylmagnesium bromide[153]. Subsequent reaction of such reagents with alkyl halides provides the appropriate α-substituted acid (equation 38).

$$PhCHMgBrCOOMgBr \xrightarrow[HMPA]{RX} PhCHRCOOH \qquad (38)$$

The dianion approach to acid synthesis has now been extended significantly by the discovery that aliphatic acids can be converted to dianions by two molecular equivalents of lithium diisopropylamide (LDA) in THF–hexane[154,155]. Alkylations of the resulting dilithio salts can be effected smoothly with alkyl halides that are not prone to undergo β-elimination (equation 39). Toluic and dimethylbenzoic acids also afford dianions, which undergo alkylation as shown in equation (40) for

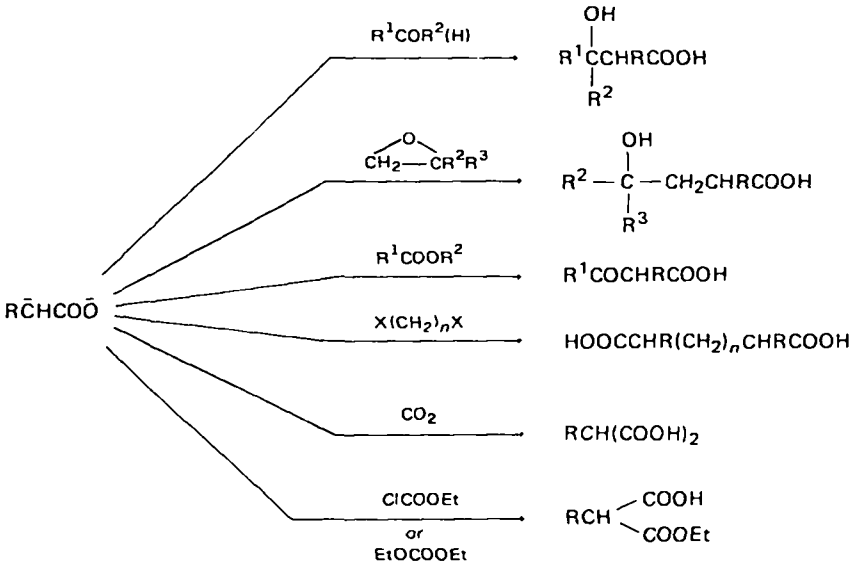
$$R^1R^2CHCOOH \xrightarrow{LDA} R^1R^2\bar{C}COO^{=} \xrightarrow{R^3X} R^1R^2R^3CCOOH \qquad (39)$$



(40)

3,4-dimethylbenzoic acid[156]. α-Anion formation can also be accomplished by initial reaction of the acid with sodium hydride in the presence of diisopropylamine, followed by addition of *n*-butyllithium[157,158].

The most generally satisfactory method for formation and alkylation of aliphatic acid dianions appears to involve the use of LDA or a combination of sodium hydride and LDA in THF–hexane[159] or THF–hexane–HMPA[159,160]. In addition to LDA, several other basic reagents can be used for dianion formation. These include lithiumnaphthalene[161-166], sodiumnaphthalene[165-70], sodiumphenanthrene[167] and lithium *t*-butyl amide[171]. Alkali amides[172] and saline hydrides[173] are not sufficiently basic to produce dianions from aliphatic acids under the mild conditions employed with LDA.



(41)

Carboxylic acid dianions serve as convenient intermediates for the synthesis of numerous types of functionalized acids (equation 41). For example, α-anions react with aldehydes and ketones to afford β-hydroxy acids[161,164,169-171,174-176], with certain epoxides to give γ-hydroxy acids and lactones[154,159] with esters to produce β-keto acids[164,178], and with dihalides (n = 2–4) to form dicarboxylic acids[154,179,180]. Carboxylation produces malonic acids[166,181], while reaction with ethyl chloroformate or carbonate esters affords alkyl hydrogen malonates[182].

Oxidation of acid dianions with molecular oxygen can afford α-hydroxy or α-hydroperoxy acids[183-185], depending on reaction conditions (equation 42).

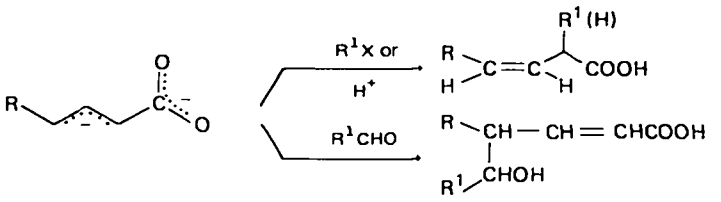
$$R^1R^2\bar{C}COO \xrightarrow{O_2} R^1R^2C(OH)COOH + R^1R^2C(OOH)COOH \quad (42)$$

$$RCH_2\bar{C}HCOO \xrightarrow{DDQ} \begin{matrix} R \\ \diagdown \\ \quad C=C \\ \diagup \quad \diagdown \\ H \quad\quad COOH \end{matrix} \quad (43)$$

When 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is used as an oxidizing agent, (*E*)-α,β-unsaturated acids are obtained in moderate yields (equation 43)[186]. Oxidative dimerization of Ivanov intermediates as well as dialkali salts of carboxylic acids can be effected with ferric chloride[187] and molecular oxygen in the presence of copper(II) salts (equation 44)[188].

$$R\bar{C}HCOO \xrightarrow[\text{or } O_2, Cu^{2+}]{FeCl_3} \begin{matrix} RCHCOOH \\ | \\ RCHCOOH \end{matrix} \quad (44)$$

Unsaturated acids containing α,β or β,γ double bonds can be converted to delocalized dianions, which undergo protonation and alkylation exclusively at the α-carbon (equation 45)[189,190]. Aldol condensations occur predominantly at the γ-position of such dianions[161,162,191].

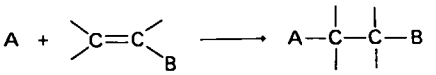


(45)

9. *Michael reactions and related conjugate additions*

Conjugate addition (Michael-type) reactions have been used to excellent advantage in the synthesis of carboxylic acids. A general review of the Michael reaction, published in 1959, includes numerous examples of this reaction in acid and ester preparations[192].

Application of Michael-type reactions to carboxylic acid synthesis takes several general forms based on the interaction of a nucleophilic addend (A) with a conjugated acceptor containing a carbanion stabilizing group (B). In certain cases



both A and B are functions which can be hydrolysed to a carboxy or carboxyalkyl group. In other instances either A or B, but not both, furnishes the carboxy or carboxyalkyl group upon hydrolysis. Hydrocyanation of diethyl benzalmalonate followed by hydrolysis to form phenylsuccinic acid (equation 46)[193] is representative of the first of these approaches. The synthesis of 3-methylheptanoic acid[194] by conjugate addition of *n*-butylmagnesium bromide to *s*-butyl crotonate illustrates the second general approach (equation 47), and also emphasizes the rather widely applicable conjugate addition of Grignard reagents to α,β-unsaturated carbonyl systems. Alkylidene malonic esters[195] and α-bromocrotonic acid[196] have been used as acceptors with Grignard reagents in similar applications of conjugate addition reactions to acid synthesis.

$$PhCH{=}C(COOEt)_2 \xrightarrow[H_2O]{KCN} PhCH(CN)CH_2COOEt \xrightarrow[H_2O]{HCl} PhCH(COOH)CH_2COOH \quad (46)$$

$$CH_3CH{=}CHCOOCHC_2H_5 \xrightarrow[2.\ hydrolysis]{1.\ n\text{-}BuMgBr} n\text{-}BuCHCH_2COOH \quad (47)$$

Conjugate addition of hydroxyl amines[197] as well as primary and secondary amines[198] to α, -unsaturated acids and esters provides a convenient route to β-amino acids.

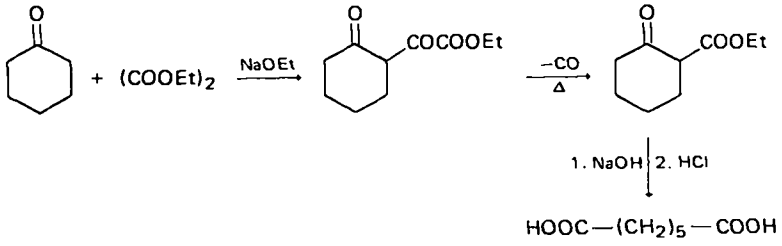
α-Anions of carboxylic acids have been found to act as Michael addends with α,β-unsaturated esters to produce half-esters of 1,5-pentanedioic acids (equation 48)[178].

$$(CH_3)_2\bar{C}COO + CH_2{=}CHCOOMe \xrightarrow[THF]{-78°C} \underset{(CH_3)_2CCOOH}{CH_2CH_2COOMe} \quad (48)$$

10. Claisen condensation

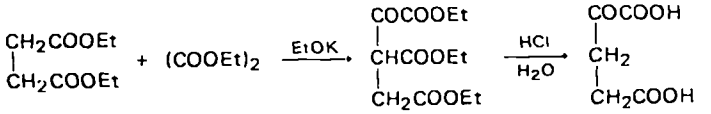
The Claisen condensation and its intramolecular counterpart, the Dieckmann reaction, are most frequently employed for the synthesis of β-keto esters and ketones[199]. However, both simple and crossed Claisen condensations have been used as key reactions in the preparation of certain carboxylic acids.

For example, pimelic acid[200] can be prepared from cyclohexanone and ethyl oxalate as shown in equation (49). The synthesis of α-ketoglutaric acid[201] is based



(49)

on initial crossed Claisen condensation of ethyl oxalate with diethyl succinate to give triethyl oxalylsuccinate, which is then hydrolysed and decarboxylated to yield the desired α-keto acid (equation 50). A recently reported method[202] for the synthesis of long-chain dicarboxylic acids involves utilization of the Claisen condensation. Thus, methyl *N,N*-dimethylsebacamate undergoes simple Claisen condensation to give *N,N,N',N'*-tetramethyl-9-carbomethoxy-10-oxononadecane diamide. Hydrolysis and decarboxylation affords 10-oxononadecanedioic acid, which is then converted to nonadecanedioic acid by Clemmensen reduction (equation 51).



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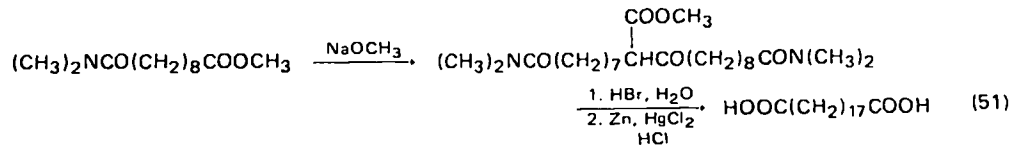
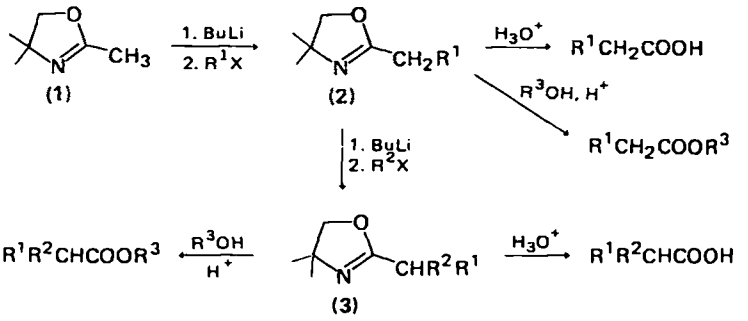


(51)

11. From oxazolines

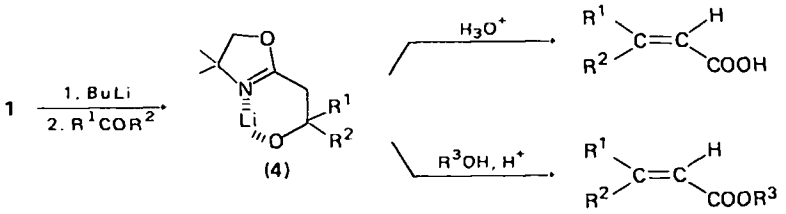
The use of heterocyclic starting materials is not often emphasized in general discussions of carboxylic acid synthesis. This problem has now been rectified by the appearance of an excellent review by Meyers[203], in which are described syntheses of acids, esters, amino acids, amides, peptides and nitriles from various heterocycles.

Among the numerous heterocyclic systems which can function as acid and ester precursors, 2-oxazolines have emerged as one of the most interesting and versatile[204]. The use of metalated 2-alkyl-2-oxazolines in the synthesis of carboxylic acids and esters is illustrated in Scheme 1[205]. Lateral lithiation of 2,4,4-trimethyl-2-oxazoline (**1**) with *n*-butyllithium at −78°C in THF, followed by alkylation of the resulting 2-lithiomethyl derivative, affords elaborated oxazolines



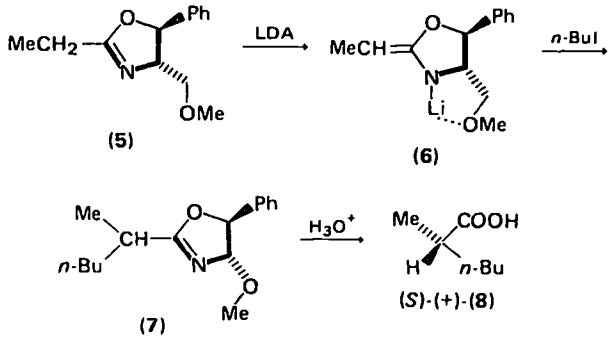
SCHEME 1.

2. Hydrolysis of 2 with aqueous hydrochloric acid then affords α-substituted acetic acids, while alcoholysis provides the corresponding esters. Sequential metalation and alkylation of 2 furnishes disubstituted oxazolines 3, which can be readily converted to α,α-disubstituted acids and esters by acid-catalysed hydrolysis and alcoholysis, respectively. It should be noted that cleavage of the oxazoline protecting group can also be effected under alkaline conditions using methyl iodide and aqueous sodium hydroxide[205]. Lithiation of 1 followed by sequential alkylation with 1,4-diiodopentane, lithiation, and a final hydrolysis step, affords a 2-methylcyclopentanecarboxylic acid as a *cis*:*trans* mixture containing 90% of the *cis* isomer[206]. If lithiation of 1 is followed by addition of an aldehyde or ketone to the reaction mixture, adducts of type 4 are produced (equation 52). Subsequent treatment of these intermediates with aqueous or alcoholic acid produces unsaturated acids and esters. Alcoholysis in the presence of very dilute mineral acid leads to formation of β-hydroxy esters[205].



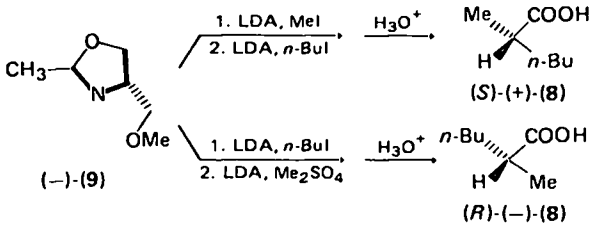
(52)

It is obvious that the synthesis of carboxylic acids via oxazoline-based routes closely resembles the α-anion approach to acid homologation. In fact, the latter procedure offers certain advantages in that starting materials are readily available and a final hydrolysis step is not necessary. However, the synthesis of chiral acids possessing high optical purity has been realized using chiral oxazolines[204,207-212], whereas the dianion method has not been employed in asymmetric synthesis. An example of such an asymmetric synthesis is illustrated in Scheme 2. In this sequence of reactions, chiral oxazoline (5), prepared by condensation of (1*S*, 2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol with the imidate of propionitrile or ethyl orthopropionate, is used as the starting material. Reaction of 5 with LDA at −78°C produces lithio derivative 6, which, upon treatment with *n*-butyl iodide, affords alkylated oxazoline 7. Hydrolysis of 7 with aqueous hydrochloric acid then provides (*S*)-(+)-2-methylhexanoic acid (8) of 66–68% optical purity[211]. Perhaps the most significant aspect of the synthesis of chiral acids from oxazolines involves the separate preparation of both enantiomers of various α-alkylalkanoic acids from



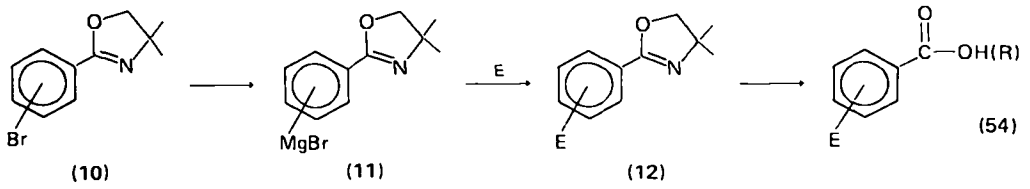
SCHEME 2.

a single chiral oxazoline[207,211]. Even more remarkable are the observations that the separate enantiomers can be prepared by varying the order of alkyl-group introduction, and that the absolute configuration of the resulting acids may be predicted prior to embarking on the synthetic scheme. Thus, introduction of the group of lower Cahn–Ingold–Prelog priority will produce acids with the (*S*) configuration, whereas initial introduction of the group of higher priority affords the acid possessing the (*R*) configuration. For example, metalation of (−)-**9** with LDA, methylation with methyl iodide, remetalation and alkylation with *n*-butyl iodide gives (*S*)-(+)-**8** possessing 70–75% optical purity (equation 53). Alternatively, if the *n*-butyl group is introduced first, followed by methylation with methyl sulphate (methyl iodide is less satisfactory), hydrolysis of the resulting dialkylated oxazoline affords (*R*)-(−)-**8** of 70% optical purity[211].



(53)

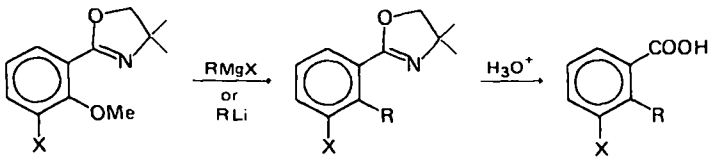
2-Aryl oxazolines have been used for the synthesis of substituted benzoic acids and esters. One such technique[213] (equation 54) involves conversion of bromo-



(54)

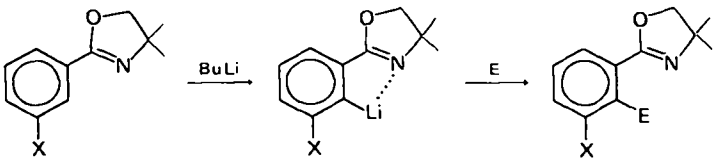
benzoic acids into the bromophenyloxazolines **10**, which are then reacted with magnesium to form Grignard reagents **11**. Condensations of **11** with various electrophiles, including aldehydes, ketones, epoxides, nitriles and deuterium oxide, produce substituted oxazolines **12**. Formation of substituted benzoic acids or benzoate esters is then accomplished by the usual methods of hydrolysis or

alcoholysis. In the case of 2-(*o*-methoxyphenyl) oxazoline the methoxy function is susceptible to nucleophilic displacement by either Grignard reagents or organolithium reagents. Completion of the reaction sequence by hydrolytic cleavage of the oxazoline masking group gives alkylbenzoic acids and diphenic acids (equation 55)[214].



(55)

Another possible application of aryloxazolines to acid synthesis is based on the finding that the oxazolinyl residue directs metalation of the aromatic ring to the *ortho* position, thereby producing a reactive site for elaboration of the aryl moiety[215]. For instance, treatment of aryl oxazolines with *n*-butyllithium affords *ortho* lithio derivatives, which react with various electrophiles (equation 56). Although hydrolysis to substituted benzoic acids was not carried out in this study, the synthetic potential is obvious.



(56)

12. *Coupling reactions*

Coupling reactions are defined here as reactions where a carbanionic species, usually an organometallic reagent, reacts with a haloester or haloacid to produce a new acid or ester. Such reactions differ from other methods discussed in this section in that the carboxy or carboalkoxy function of the product is furnished by the electrophilic component of the reaction rather than by the carbanion.

Grignard reagents undergo coupling reactions with THF-soluble chloromagnesium salts of ω-bromo acids in the presence of catalytic amounts of dilithium tetrachlorocuprate (equation 57)[216]. Carboxylic acid esters can be synthesized in a

$$RMgBr + Br(CH_2)_nCOOMgCl \xrightarrow[2.\ H_3O^+]{1.\ Li_2CuCl_4} R(CH_2)_nCOOH \qquad (57)$$

related fashion by reaction between copper(I) 'ate' complexes, formed from methylcopper(I) and primary or secondary Grignard reagents, and esters of primary iodoalkylcarboxylic acids[217]. For example, ethyl 21-docoseneoate can be prepared in 79% yield from methyl (10-undecenyl)cuprate and ethyl 11-iodoundecanoate

$$CH_2{=}CH(CH_2)_8CH_2Cl \xrightarrow[2.\ (MeCu(I))]{1.\ Mg,\ THF} CH_2{=}CH(CH_2)_8CH_2\underset{\displaystyle Me}{\underset{|}{C}}uMgCl$$

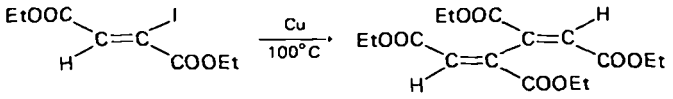
$$\xrightarrow[THF]{I(CH_2)_{10}COOEt} CH_2{=}CH(CH_2)_{19}COOEt \qquad (58)$$

(equation 58). Diarylcadmium reagents have been reported to undergo coupling with α-bromo esters to give phenylacetic esters (equation 59)[218]. α-Bromo esters undergo dimerization in the presence of zinc and copper(II) chloride to afford succinate esters (equation 60)[219]. Ullman-type coupling of diethyl iodofumarate

$$Ar_2Cd + BrCHRCOOEt \longrightarrow ArCHRCOOEt \tag{59}$$

$$R^1R^2\overset{Br}{\underset{|}{C}}HCOOR^3 \xrightarrow[THF]{Zn-CuCl_2} R^3OOC-\overset{R^1}{\underset{R^2}{C}}-\overset{R^1}{\underset{R^2}{C}}COOR^3 \tag{60}$$

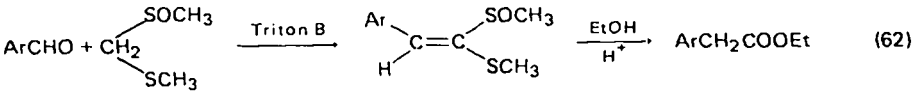
occurs with copper powder to afford pure *trans,trans*-1,2,3,4-tetracarboethoxy-1,3-butadiene in 96% isolated yield (equation 61)[220]. A similar reaction with diethyl iodomaleate affords 89% of the analogous butadiene consisting of 87% of the *cis,cis* ester and 13% of the *trans* isomer. Evidence was presented in this study to show that the products were formed by coupling of organocopper intermediates.



(61)

13. *Miscellaneous condensation reactions*

a. Carbanion reactions. Two recent synthetic methods involving carbanionic intermediates are worthy of note. In the first of these, the carbanion derived from the synthetically versatile reagent, methylsulphinylmethyl methyl sulphide (13)[221], is allowed to react with aryl aldehydes. The resulting 1-methylsulphinyl-1-methylthio-2-arylethylenes (14) afford α-substituted acetate esters upon ethanolysis (equation 62)[222]. A related procedure, also leading to α-substituted acetic acid esters, involves acylation of 13 with esters, followed by sodium borohydride reduction, acetylation, elimination and hydrolysis of the resulting unsaturated derivatives 14[223].

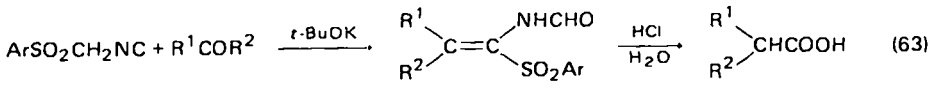


(62)

(13) (14)

The second procedure involves condensation of isocyanomethyl aryl sulphones (15) with aliphatic and aromatic aldehydes and ketones to give *N*-(1-arylsulphonyl-1-alkenyl) formamides (16), which can be hydrolysed to carboxylic acids containing one more carbon than the starting carbonyl compound (equation 63)[224,225].

Both of the foregoing methods provide a convenient route to saturated acids through active hydrogen condensations, whereas most related reactions

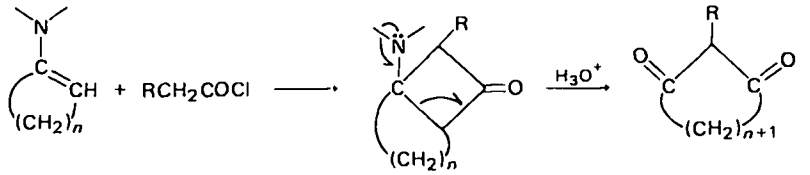


(63)

(15) (16)

(Knoevenagel, Doebner, Stobbe), involving active methylene components, afford unsaturated acids.

b. From enamines. A rather general method for the synthesis of long-chain acids involves reaction of enamines derived from cyclic ketones with an aliphatic acid chloride in the presence of the triethylamine. The resulting cyclobutanone derivative undergoes ring-opening during hydrolysis to form 2-alkyl-1,3-cycloalkanediones, which are then cleaved to keto acids. Reduction of the keto acids provides the saturated acid (equation 64)[226,227]. It should be noted that this scheme works best with enamines derived from cyclic ketones containing more than nine carbon atoms.



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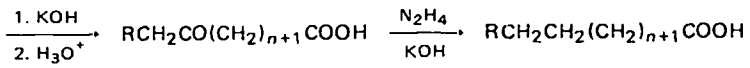


C. Acids by Free-radical Processes

The two types of radical reactions used most frequently for the synthesis of carboxylic acids involve either addition of radical species to unsaturated compounds or radical substitution on aromatic substrates. Radical additions represent the more versatile approach, and appear in subsequent sections of this chapter in connection with the preparation of other types of acid derivatives.

1. Radical additions to unsaturated systems

The use of radical additions for the synthesis of acids and acid derivatives has been reviewed[228]. The basic approach involves radical-chain addition of an α-carboxyalkyl radical to an olefinic substrate, to give an acid in which the nature of X depends upon the source of the radical addend (equation 65). If the radical is

(65)

generated from an α-bromo ester, X is bromine; with unsubstituted acids and esters, as well as α-chloro esters, X is hydrogen. Carboxyalkyl radicals are derived from carboxylic acids containing at least one α-hydrogen upon treatment with an appropriate initiator. The most efficient chemical initiators appear to be di-*t*-butyl peroxide (DTBP) and dibenzoyl peroxide (DBP), although several other peroxides of comparable thermal stability have been employed. The nature of the unsaturated component has a strong bearing on the success of these reactions, with terminal olefins serving as the most satisfactory acceptors for carboxyalkyl radical. Free-radical polymerization of other types of olefins may be a serious competing reaction.

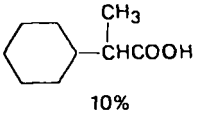
The general procedure employed for these reactions usually involves treatment of the olefin with a 10- to 100-fold molar excess of the carboxylic acid in the presence of a catalytic amount (ca 5–25 mol percent) of initiator at reflux. The

syntheses (equation 66) of *n*-decanoic acid[229,230], 2-methyldecanoic acid[231], 2,2-dimethyldodecanoic acid[231-233] and 2-cyclohexylpropanoic acid[234] are representative of the approach. Comparison of yields obtained in these reactions reveals the effect of both acid and olefin structure on the efficiency of the process.

$$n\text{-}C_6H_{13}CH{=}CH_2 + CH_3COOH \xrightarrow{DTBP} n\text{-}C_8H_{17}CH_2COOH \quad 60\text{–}70\% \tag{66a}$$

$$n\text{-}C_6H_{13}CH{=}CH_2 + CH_3CH_2COOH \xrightarrow{DTBP} n\text{-}C_8H_{17}CH(CH_3)COOH \quad 60\text{–}75\% \tag{66b}$$

$$n\text{-}C_8H_{17}CH{=}CH_2 + CH_3CH(CH_3)COOH \xrightarrow{DTBP} n\text{-}C_{10}H_{21}C(CH_3)_2COOH \quad 36\% \tag{66c}$$


+ CH_3CH_2COOH $\xrightarrow{DTBP}$

10% (66d)

2. *Carboxyalkylation of aromatic compounds*

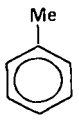
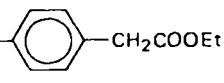
Generation of carboxymethyl radicals in the presence of suitable aromatic substrates results in homolytic substitution leading to arylacetic acids (equation 67). This process, which is referred to as aromatic carboxymethylation, has been the subject of a recent review[235].

$$Ar{-}H + \dot{C}H_2COOH \longrightarrow ArCH_2COOH \tag{67}$$

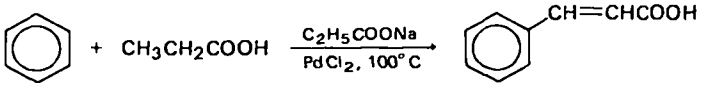
Carboxymethylations can be effected thermally with chloroacetic acid (in the presence of iron salts and/or potassium bromide), with bromoacetic acid, or with chloroacetylpolyglycolic acid. Thermally induced carboxymethylations proceed reasonably well with certain fused ring aromatics, but simple benzene derivatives do not react.

Oxidative carboxymethylation of aromatic compounds, including several mono- and disubstituted benzenes, has been accomplished using acetic acid or acetic anhydride as the radical source. Oxidizing agents which can be used to generate carboxymethyl radicals in such reactions include potassium permanganate, manganese(III) acetate, cerium(IV) acetate, diacetyl peroxide and DTBP.

Photochemical carboxymethylations have been employed in a limited number of cases. Satisfactory precursors for carboxymethyl radicals in these reactions include iodoacetic acid, thioglycolic acid and ethyl chloroacetate. Photochemical reactions appear to be the most satisfactory for carboxymethylation of simple aromatics. For example ethyl *p*-methylphenylacetate can be prepared from toluene and ethyl bromoacetate by photolysis in the presence of zinc chloride (equation 68)[236].


+ $BrCH_2COOEt$ $\xrightarrow[ZnCl_2]{h\nu}$ Me  CH_2COOEt (68)

Aromatic carboxyvinylation can be realized in moderate yields by reacting aliphatic acids possessing α- and β-hydrogens with an appropriate aromatic substrate in the presence of palladium(II) salts and alkali metal carboxylates[237]. For example, treatment of benzene with propionic acid and sodium propionate in the presence of palladium(II) chloride gives cinnamic acid in 28% yield (equation 69).

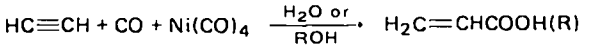


(69)

D. Acids by Hydrocarboxylation Reactions

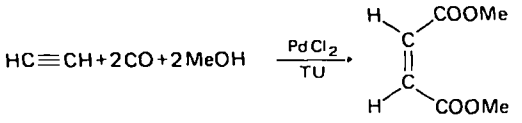
Hydrocarboxylations are classified here as reactions in which the –COOH group is introduced by treatment of organic molecules with carbon monoxide in the presence of an appropriate catalyst. Although such reactions have been valued primarily for their industrial applications, recent developments in the area of transition metal catalysis now permit hydrocarboxylations to be carried out at ambient temperatures with low carbon monoxide pressure. Several excellent reviews summarizing reactions of carbon monoxide with various organic compounds have appeared[238-241]. One of these[240] is devoted specifically to the synthesis of carboxylic acids and esters under mild conditions. The present discussion is meant to outline some of the more important hydrocarboxylation procedures which can be conducted under normal laboratory conditions. Since preparations of acids and esters are generally quite similar, both types of compounds are discussed here.

Acetylenes and olefinic compounds readily yield to hydrocarboxylation, affording unsaturated and saturated acids (esters), respectively. For example the Reppe synthesis[242] of acrylic acid and its esters is accomplished by reaction of acetylene with carbon monoxide in the presence of nickel tetracarbonyl and water, or a mixture of water and alcohol (equation 70). Treatment of acetylene with



(70)

carbon monoxide using palladium chloride complex with thiourea (TU) in methanol affords dimethyl maleate in excellent yield (equation 71)[243]. Although hydrocarboxylation of substituted acetylenes may lead to complications[238-241] too numerous to mention in this review, it is possible in some instances to effect reasonably good regiospecificity in the production of unsaturated acids as illustrated in equation (72)[244].



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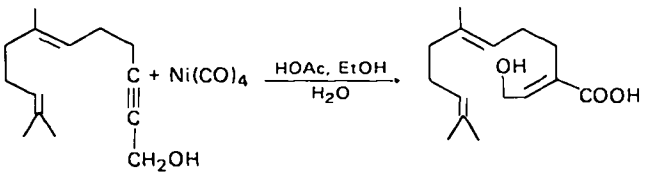
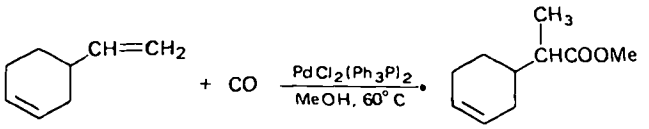


(72)

Olefinic substrates normally require more rigorous conditions for hydrocarboxylation than alkynes. However, the synthesis of acids from olefins can be effected smoothly at atmospheric pressure and room temperature using nickel tetracarbonyl in the presence of organic acids (equation 73)[245]. Olefins can also be carbonylated at low temperature employing palladium chloride complexed with triphenylphosphine[246] as shown for 4-vinylcyclohexene (equation 74). However,

$$RCH{=}CH_2 + CO + H_2O \xrightarrow[R^1COOH]{Ni(CO)_4} \underset{\text{major}}{RCH(CH_3)COOH} + \underset{\text{minor}}{RCH_2CH_2COOH} \quad (73)$$



(74)

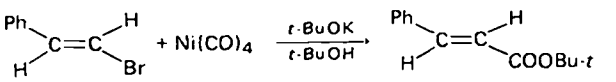
these reactions require carbon monoxide pressures of 300–700 atmospheres. Recently[247-248], linear, rather than branched, esters have been obtained by carbonylation of α-olefins using ligand-stabilized platinum(II)–group 4B metal halide complexes[247] or ligand-stabilized palladium(II)–group 4B metal halide complexes[248]. In spite of the high degree of regiospecificity, these reactions also require rather high (>100 atm) carbon monoxide pressures. Carbonylation of olefins can be carried out at room temperature and atmospheric pressure using a copper(I) carbonyl catalyst in concentrated sulphuric acid[249]. These processes give mixtures of tertiary acids resulting from extensive rearrangement of the carbonium ions formed in the reaction medium.

Organic halides furnish carboxylic acids and esters upon carbonylation. Allylic halides can be converted to β,γ-unsaturated esters by treatment with carbon monoxide in the presence of nickel π-allyl complexes (equation 75)[250]. Benzylic

$$CH_2{=}C(CH_3)CH_2Cl + CO + MeOH \xrightarrow[\text{complex}]{Ni\ \pi\text{-allyl}} CH_2{=}C(CH_3)CH_2COOMe \quad (75)$$

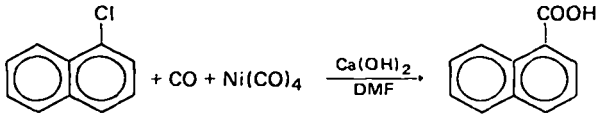
halides are transformed into phenylacetic acids and esters in good yields by nickel tetracarbonyl-catalysed carbonylation in DMF if iodide ion and a basic reagent, such as calcium oxide or triethylamine, are present (equation 76)[251]. Vinyl halides can be carbonylated to form α,β-unsaturated esters with retention of stereochemistry about the double bond by means of nickel tetracarbonyl in *t*-butyl alcolol containing potassium *t*-butoxide (equation 77)[252], or in methanol containing sodium methoxide[253]. These reactions do not require addition of exogeneous carbon monoxide.

$$PhCH_2Cl + CO + H_2O \xrightarrow[CaO,\ DMF]{Ni(CO)_4,\ I^-} PhCH_2COOH \quad (76)$$



(77)

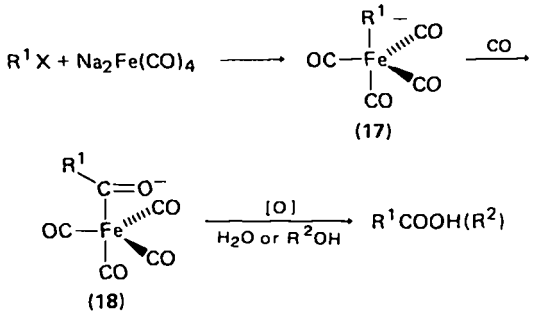
A recent example of facile hydrocarboxylation of aryl halides involves reactions employing nickel tetracarbonyl and calcium hydroxide in polar aprotic solvents



(78)

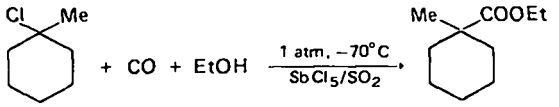
(equation 78)[254]. Aryl and vinylic bromides and iodides as well as benzyl chloride react with carbon monoxide and alcohols in the presence of tertiary amines and palladium–triphenylphosphine to form esters in good yields[255]. Simple alkyl halides and/or tosylates with sodium tetracarbonyl ferrate(−II) to give alkyltetracarbon monoxide and cobalt carbonyl anion in methanol containing a tertiary amine base[256].

An interesting procedure[257] leading to acids and esters is based on treatment of halides and/or tosylates with sodium tetracarbonyl ferrate(−II) to give alkyltetracarbonyliron(I) complexes (**17**), which react with carbon monoxide to afford acyl complexes (**18**) (equation 79). Oxidation of either type complex with oxygen or aqueous sodium hypochlorite affords acids in good yield. When oxidation is carried out in alcohol solution the corresponding esters are obtained.



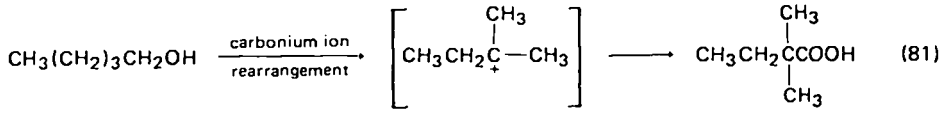
(79)

Carbonylation of tertiary alkyl halides can be effected with carbon monoxide in liquid SO_2 using antimony pentafluoride (equation 80)[258].



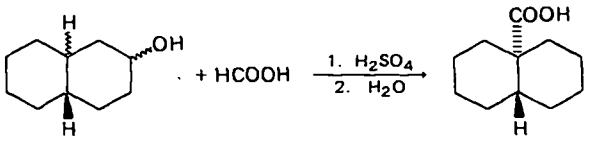
(80)

Alcohols can serve as useful starting materials for carboxylic acids under reaction conditions favouring carbonium ion formation. It should be noted that in many such reactions, rearrangement of the initially generated primary and secondary carbonium ions occurs to give tertiary carboxylic acids and esters. For example, treatment of 1-pentanol in 98% sulphuric acid with carbon monoxide in the presence of copper(I) oxide affords 2,2-dimethylbutanoic acid as the major product (equation 81)[259]. Similarly, 2-hydroxydecalin yields *trans*-9-decalincarboxylic acid



(81)

upon treatment with formic acid in concentrated sulphuric acid at 0°C (equation 82)[260,261]. This conversion is an example of the Koch–Haaf reaction[262,263] in



(82)

which an alcohol or alkene serves as the carbonium ion precursor, and formic acid is the source of carbon monoxide. A recent report describes the hydrocarboxylation of alcohols using carbon monoxide in the presence of hydrogen fluoride and antimony pentafluoride[264].

An interesting method for the synthesis of *N*-acylamino acids is based on carbonylation of *N*-(hydroxymethyl)-amides or imides with carbon monoxide or formic acid in sulphuric acid[265,266]. The preparation of hippuric acid is illustrative of this procedure (equation 83).

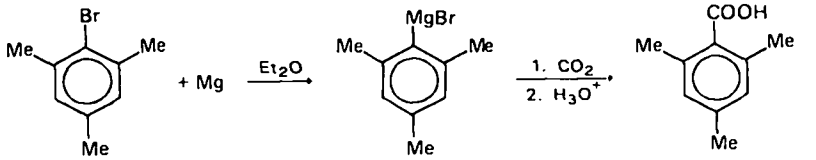
$$PhCONHCH_2OH + CO \xrightarrow[2.\ H_2O]{1.\ H_2SO_4,\ HOAc} PhCONHCH_2COOH \qquad (83)$$

Alkanes containing tertiary hydrogens can be carbonylated by allowing them to react with formic acid or carbon monoxide and an alcohol or alkene in sulphuric acid. The alcohol or alkene is converted to a carbonium ion which then abstracts a hydride ion from the alkane to form a new cation. This cation reacts with carbon monoxide to yield the acid derived from the saturated substrate. 1-Adamantanecarboxylic acid[267] is synthesized in this way. Carbonylation of saturated hydrocarbons has also been accomplished with carbon monoxide and an alkene or alcohol in sulphuric acid using copper(I) carbonyl as the catalyst[268].

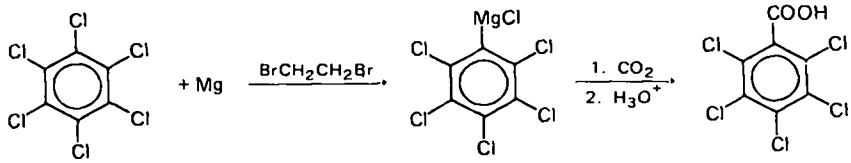
E. Acids by Carbonation of Organometallic Reagents

Reaction of organometallic reagents with carbon dioxide is a versatile and widely used method for carboxylic acid synthesis. Fundamental considerations of this method, along with numerous examples of its application to the synthesis of mono- and dicarboxylic acids, have been reviewed[269].

Of the numerous types of organometallics which can be carbonated to form acids, Grignard reagents and organolithium reagents are used most frequently because of the facility with which they can be prepared by halogen–metal exchange or by direct metalation (equation 84)[270,271]. The syntheses of mesitoic acid[272] and pentachlorobenzoic acid (equation 85)[273] represent typical Grignard

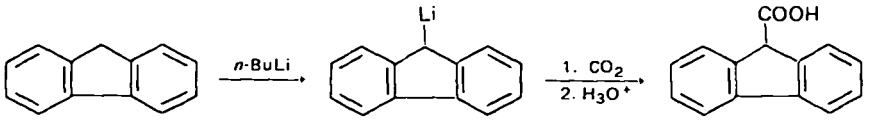


(84)

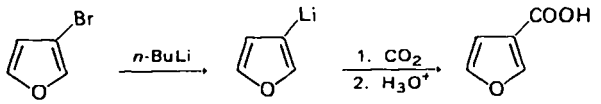


(85)

carbonations. The use of ethylene bromide, as shown in equation (85), accelerates the formation of Grignard reagents from aryl chlorides. The synthesis of fluorene 9-carboxylic acid is representative of the formation and carbonation of organolithium reagents derived from acidic hydrocarbons (equation 86)[274]. The recently reported preparation of 3-furoic acid[275] is typical of the procedures used to prepare aromatic acids from aryl halides via initial halogen–metal exchange (equation 87).

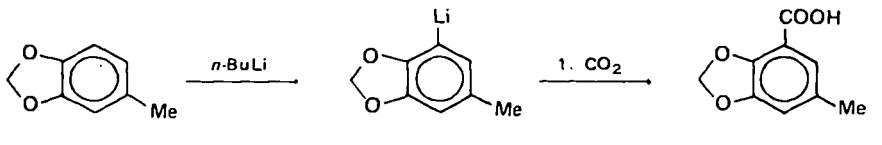


(86)



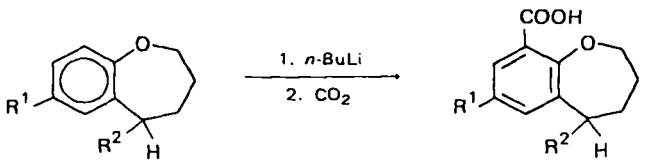
(87)

Aryllithium reagents suitable for carbonation can also be prepared by direct ring metalation of benzene derivatives containing one or more alkoxyl functions. Lithiation is directed exclusively *ortho* to the ether function. Equations (88)–(90) are typical of *ortho* lithiation followed by carbonation. Note that lithiation of 3,5-dimethoxyfluorobenzene is accompanied by replacement of fluorine.

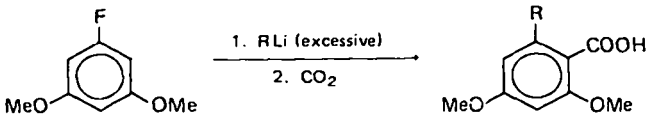


(Ref. 276)

(88)



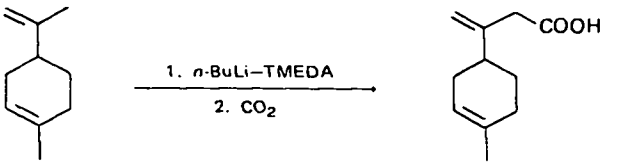
(Ref. 277) (89)



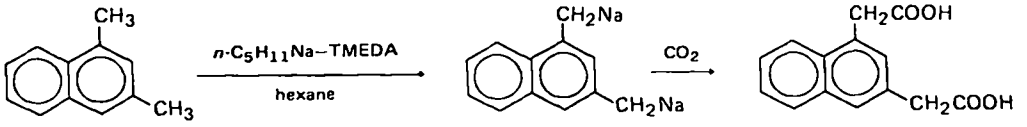
(Ref. 278) (90)

An interesting development associated with the preparation of organolithium reagents for carbonation is the discovery that certain alkenes undergo allylic lithiation by means of the powerful metalating agent formed by complexation of *n*-butyllithium with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[279]. Thus, treatment of limonene with *n*-butyllithium–TMEDA followed by carbonation produces the β,γ-unsaturated acid derived from lithiation at $C_{(10)}$ (equation 91)[280]. Although the generality of this approach has yet to be fully determined, it would appear to offer a decided advantage over more conventional methods for allylic metalation, which usually employ organosodium reagents[281,282].

Recently, it has been found that dimethylarenes such as 1,3-dimethylnaphthalene can be dimetalated with *n*-amylsodium complexed with TMEDA to produce disodio derivatives, which are carbonated to form dicarboxylic acids (equation 92)[283].

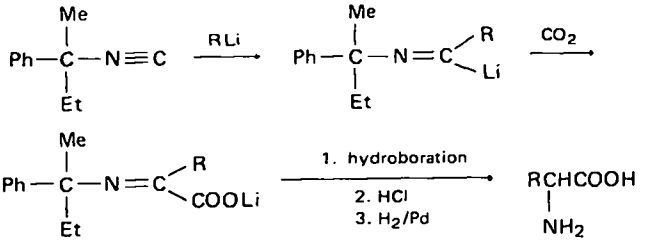


(91)



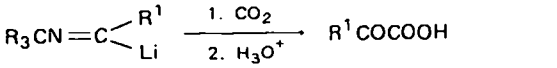
(92)

Carbonation of lithium aldimines, formed by addition of alkyllithium reagents to isocyanides, produces α-imino acids, which can be reduced and debenzylated to afford α-amino acids (equation 93)[284]. Use of optically active isocyanides leads to

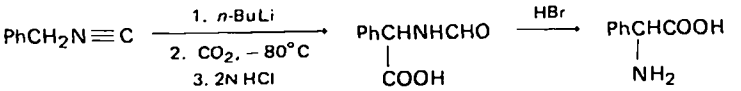


(93)

production of amino acids of reasonably high optical purity. In a related series of reactions, lithium aldimines have been carbonated, and the intermediate α-imino acids hydrolysed to α-keto acids (equation 94)[285]. Reaction of organolithium reagents with isocyanides containing α-hydrogens results in formation of α-lithio derivatives, which can be carbonated to give *N*-formyl α-amino acids. Subsequent hydrolysis of the *N*-formyl group produces free amino acids (equation 95)[286].

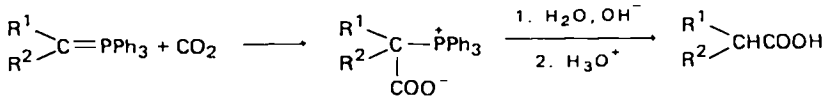


(94)



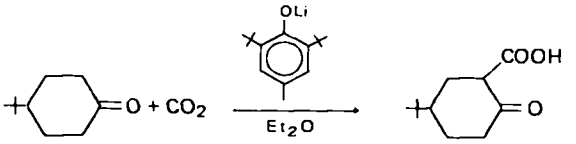
(95)

Carbonation of phosphoranes represents an efficient new method for acid preparation (equation 96)[287].



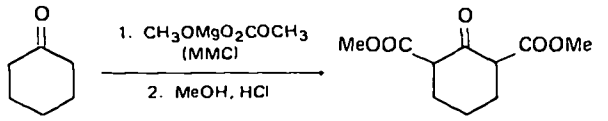
(96)

The synthesis of β-keto acids by carbonation of ketones can be effected in good yields using the hindered base, lithium 4-methyl-2,6-di-*t*-butylphenoxide (equation 97)[288]. This reagent is also useful for carbonation of acetylenes and sulphones[288]. Iron(III) ethoxide in DMF has also been found to be an effective base for α-carbonation of ketones[289].

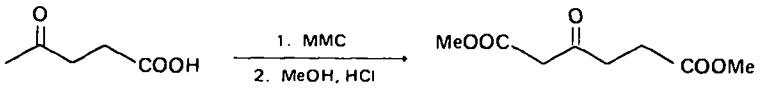


(97)

Several recent reports have further confirmed the utility of methyl magnesium carbonate[290] (MMC) as an excellent reagent for carboxylation of carbonyl compounds, including cyclohexanone (equation 98)[290], levulinic acid (equation 99)[291], and γ-butyrolactones (equation 100)[292]. γ- and δ-Lactones also undergo α-carboxylation upon treatment with LDA in THF at −78°C, followed by addition of carbon dioxide to the reaction mixtures[293].



(98)



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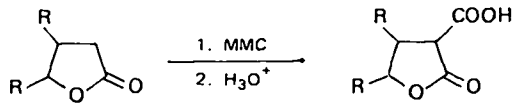


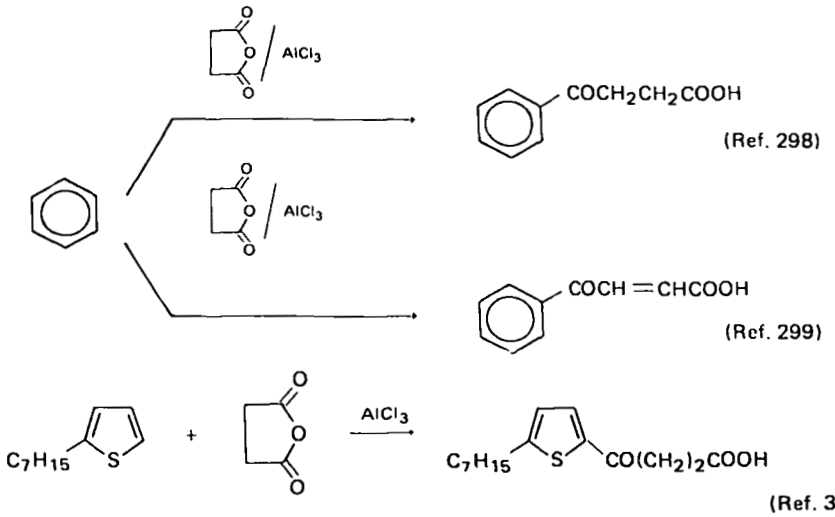
(100)

Ring carboxylation of alkali metal salts of resorcinol and α-naphthol can be accomplished with carbon dioxide under conditions of the Kolbe–Schmitt reaction[294]. An interesting modification of this reaction employs MMC as the carboxylating agent[295]. Carboxylation of certain aromatic systems has been realized using the mixture acetic acid–acetic anhydride–sodium acetate in the presence of palladium chloride[296].

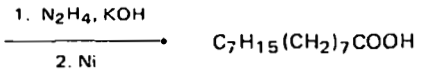
F. Acids by Electrophilic Substitution Reactions

A classical method of acid synthesis by electrophilic substitution involves acylation of an appropriate aromatic substrate with a dibasic acid anhydride in the presence of a Lewis acid catalyst[114,115]. Several typical examples are shown in equations (101) and (102). The last of these includes both reduction of the ketone function, a common procedure for synthesizing ω-aryl acids, and reductive desulphurization of the thiophene ring, a useful method for homologation of carboxylic acids.

Aromatic acids and esters can be prepared by Friedel–Crafts-type reactions using various derivatives of carbonic acid[301]. For example, reaction of mesitylene

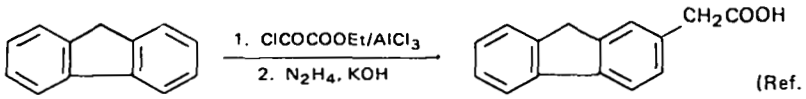


(101)



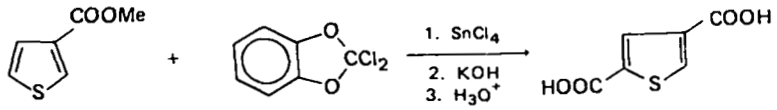
(102)

with oxalyl chloride in the presence of aluminium chloride yields mesitoic acid[302]. Phosgene[303] can also be used to prepare benzoic acids, while ethyl oxalyl chloride affords α-keto acids, which can be converted to arylacetic acids by reduction (equation 103)[304]. Pyrocatechol dichloromethylene acetal[305] is a useful reagent



(103)

for introduction of aromatic carboxyl groups, as illustrated in the synthesis of 2,4-thiophenedicarboxylic acid (equation 104)[306]. Trichloroacetyl chloride reacts with pyrrole to give 2-trichloroacetylpyrrole, which can then be converted to the ethyl ester of 2-pyrrolecarboxylic acid by treatment with sodium ethoxide (equation 105)[307].



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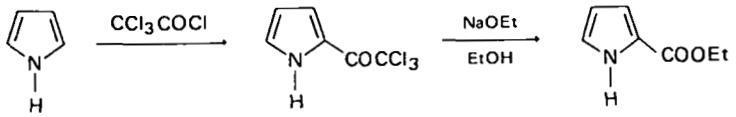


(105)

G. Acids by Oxidation Reactions

The preparation of acids and esters can be accomplished by the oxidation of a number of functional groups using a wide variety of reagents. In this section the

preparation of acids and esters is primarily categorized in terms of the functionality of the starting material and subsequently in terms of the oxidizing agent used. Since two comprehensive discussions of the oxidation mechanisms using a wide variety of oxidizing agents has been published[308,309], a detailed discussion of this aspect of the oxidation will not be attempted in this review.

1. *Oxidation of alcohols*

Only one general review[310] has been published on the oxidation of alcohols and it is specifically concerned with *Phenyl Derivatives of Dihydric and Polyhydric Alcohols and Their Oxidation Products.*

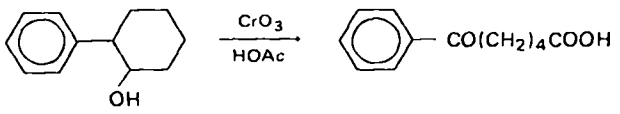
a. With base. Although not considered a major reaction for the oxidation of alcohols to acids, treatment of alcohols with base at high temperature has been reported to oxidize alcohols to acid in good to excellent yields in at least two cases[311,312]. In the oxidation of hydrocinnamyl alcohol-d to hydrocinnamic acid-d, treatment with KOH at 245–255°C followed by acidification was used to effect the conversion in 88% yield[311]. Sodium hydroxide at 340–360°C and 50–500 atm has been used[312] to convert terminal alkanediols into sodium alkane dicarboxylates in yields ranging from 50 to 75% (equation 106).

$$HOCH_2-CH_2OH + NaOH \xrightarrow[300°C,\ 400\ atm]{heat} Na^+\,\bar{O}OC-C\bar{O}O\,Na^+ \quad (75\%) \qquad (106)$$

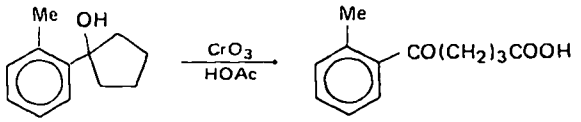
b. With hypochlorite. A rather interesting oxidation is the reaction of an excess of isoamyl alcohol with *t*-butylhypochlorite in carbon tetrachloride which leads to an 89% yield of isoamylisobutylate (equation 107)[313].

$$Me_2CHCH_2CH_2OH + Me_3COCl \xrightarrow{CCl_4} Me_2CHCH_2COOCH_2CH_2CHMe_2 \qquad (107)$$

c. With oxides of chromium. The oxides of chromium in a variety of solvents have been one of the most common oxidizing systems used to convert alcohols to acids. Chromium trioxide in acetic acid has been used to effect the conversion of 10-fluorodecanol to 10-fluorodecanoic acid[314], 1-phenyl-1-cyclohexanol to δ-benzoylvaleric acid (equation 108)[315,316] and 1-(*o*-tolyl)cyclopentanol to γ-(2-methylbenzoyl)butyric acid (equation 109)[317].



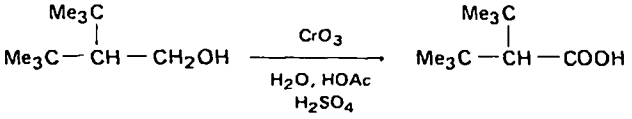
(108)



(109)

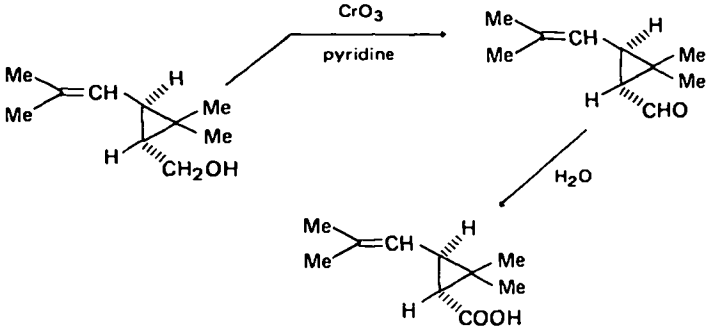
When chromium trioxide is dissolved in water and acetic acid is added the resulting oxidizing agent is chromic acid. This reagent has been used in sulphuric acid, to convert 2,2-di-*t*-butylethanol into di-*t*-butylacetic acid (equation 110)[318], and in acetone, to convert the isomeric tetrahydropyranyloxy-2,2,4,4-

tetramethylcyclobutan-1-carbinols into their corresponding isomeric hydroxy acids[319]. This reaction represents a unique cleavage of a hydroxy protecting group without additional oxidation.



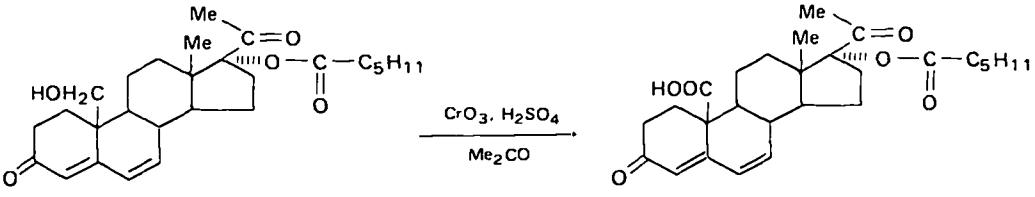
(110)

One indication of the difference in oxidizing ability of chromium trioxide and chromic acid can be seen from the work of Mills, Murray and Raphael[320], who found that oxidation of chrysanthemyl alcohol at room temperature with chromium trioxide in dry pyridine afforded the corresponding aldehyde; however, upon the addition of water, the oxidation process was allowed to continue further to produce (±)-*trans*-chrysanthemic acid (equation 111). Similar oxidation of the allenic alcohol, 2,2-dimethyl-3-(2-methylprop-1-enylidene)cyclopropylmethanol, afforded dehydrochrysanthemic acid[320].



(111)

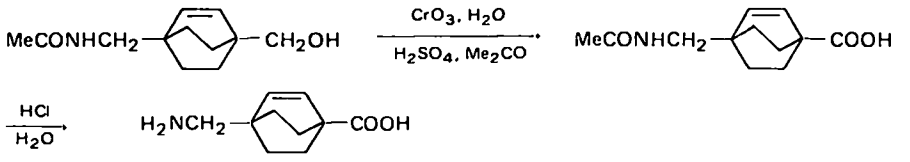
Addition of chromium trioxide to water and sulphuric acid produces Jones' reagent, which has been used in acetone to effect the oxidation of the steroid shown in equation (112) to its corresponding acid[321], and of 1-acetamidomethyl-4-hydroxymethylbicyclo[2.2.2]oct-2-ene to 4-acetamidomethylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, which upon hydrolysis with hydrochloric acid affords 4-aminomethylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid (equation 113)[322].



(112)

t-Butyl chromate has been used to oxidize hexadecanol to hexadecanoic acid in 54% yield[323].

With sodium dichromate as the oxidizing agent it is very common to find an ester as the product of alcohol oxidation, as in the oxidation of *n*-butyl alcohol which affords *n*-butyl *n*-butyrate (equation 114)[324].



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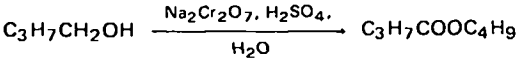
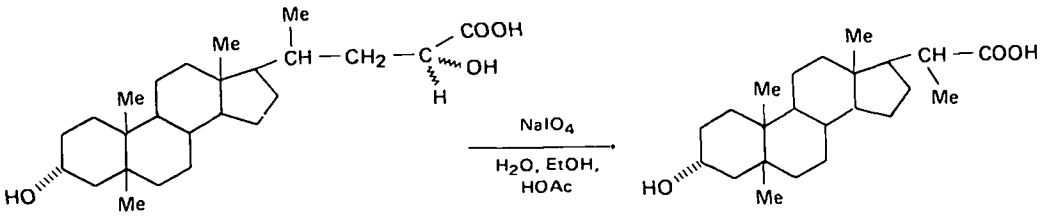


(114)

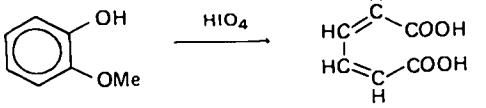
d. With periodic acid and periodates. The use of metaperiodic acid (HIO_4), sodium metaperiodate ($NaIO_4$) and paraperiodic acid (H_5IO_6) as oxidizing agents in organic and bio-organic chemistry has recently been reviewed[325].

Periodate oxidative cleavage of the α-hydroxy acid side-chain in the bile acid 3α,22-dihydroxycholanic acid in a water–ethanol–acetic acid solution affords norcholanic acid (equation 115)[326].



(115)

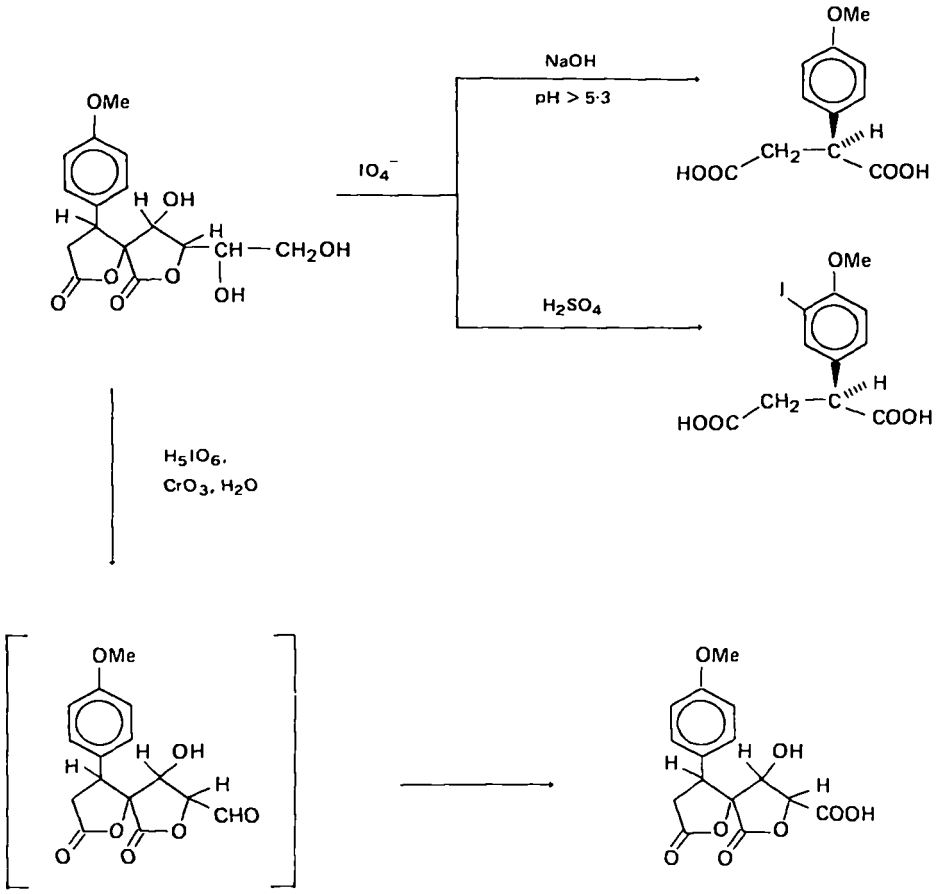
The reaction of periodic acid itself as an oxidizing agent has also been reported. With guaiacol the reaction has been reported[327] to yield *o*-benzoquinone and *cis,cis*-muconic acid, obtained by further cleavage of the *o*-benzoquinone initially formed (equation 116).



(116)

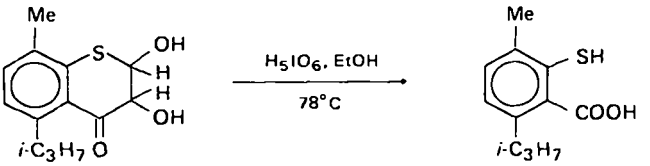
Application of periodate and periodic acid oxidations to the field of natural products is exemplified by the work of Perold and coworkers[328], (Scheme 3) who treated the dilactone canocarpin methyl ether (naturally occurring from the dried leaves of *Leucospermum conocarpodendron*, South Africa) with sodium periodate at pH >5.3 and with orthoperiodic acid in sulphuric acid. The dilactone, which has the 4*S*, 5*S*, 8*R*, 9*R*, 10*S* configuration, was found to have four of its chiral centres destroyed during the reaction and gave (+)-*p*-methoxyphenylsuccinic acid with a 4S configuration at pH >5.3 using sodium periodate, and (+)-(3-iodo-4-methoxyphenyl)succinic acid under acid conditions using orthoperiodic acid. However, when the same compound was oxidized with a mixture of paraperiodic acid and chromium trioxide in water, the primary–secondary glycol function was degraded to the carboxy group in 85% yield via an intermediate aldehyde[329]

An example of oxidative thio ring-opening using paraperiodic acid has been reported[330] in a preparation of a mercaptocumenecarboxylic acid. Refluxing a solution of 2,3-dihydro-2,3-dihydroxy-5-isopropyl-8-methyl-1-thianaphthalene-4-



SCHEME 3.

one with paraperiodic acid in 95% ethanol afforded a crude product which was warmed for two hours with aqueous 10% sodium hydroxide to give 3-mercapto-4-methyl cumene-2-carboxylic acid in 87% yield.



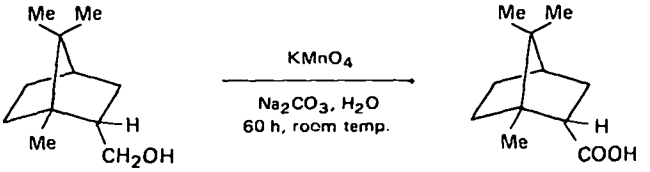
(117)

e. With oxides of manganese. Both acidic and basic solutions of potassium permanganate have been used successfully to oxidize alcohols to carboxylic acids. For example, reaction of 5,5,5-trichloropentanol with an acidic solution of potassium permanganate afforded δ,δ,δ-trichloropentanoic acid in 92% yield[331] while treatment of isobutyl alcohol with basic potassium permanganate afforded isobutyric acid in 84% yield (equation 118)[332]. This method has also been used to

$$Me_2CHCH_2OH \xrightarrow[Na_2CO_3]{KMnO_4} Me_2CHCOOH \qquad (118)$$

prepare[332] *n*- and *iso*-valeric, *n*-hexoic, *n*-heptoic and enanthylic acids from their corresponding alcohols.

Bicyclic systems have also been oxidized using potassium permanganate without destruction of the bicyclic skeleton, as illustrated by the room-temperature conversion of *endo*-2-hydroxymethylbornane to *endo*-2-bornane carboxylic acid in 66% yield using a sodium carbonate solution of permanganate[333].

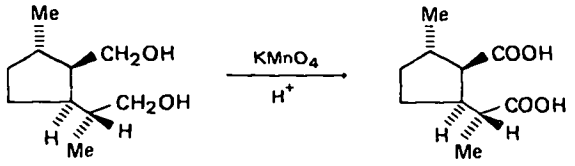


(119)

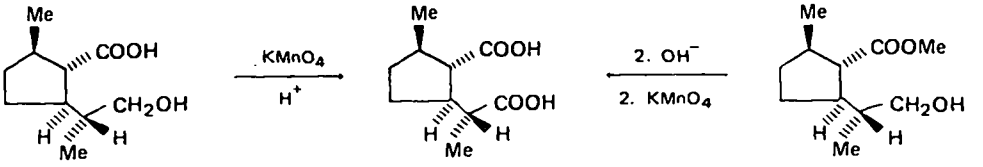
Silanes have also been oxidized using potassium permanganate without any destruction of the silicon–carbon bond, as indicated by the conversion of dimethyl bis(3-hydroxypropyl)silane to its corresponding dibasic acid (equation 120)[334].

$$Me_2Si(CH_2CH_2CH_2OH)_2 \xrightarrow{KMnO_4} Me_2Si(CH_2CH_2COOH)_2 \qquad (120)$$

That alcohols can be oxidized to carboxylic acids using potassium permanganate in acid or base without effecting the stereochemistry of the molecule is illustrated by the work of Ficini and Angelo[335], shown in equations (121) and (122).

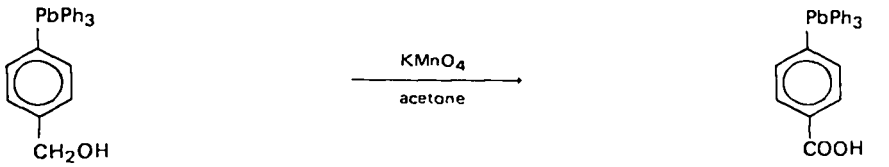


(121)

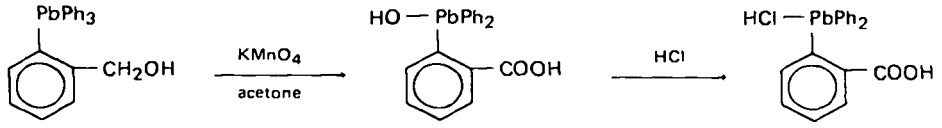


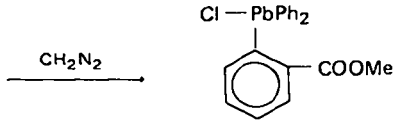
(122)

The use of potassium permanganate oxidation of alcohols to acids has been extended to organometallic systems with interesting results[336]. Permanganate oxidation of (*p*-hydroxymethylphenyl)triphenyllead in acetone gave (*p*-carboxyphneyl)triphenyllead in 25% yield (equation 123). However, treatment of (*o*-hydroxymethylphenyl)triphenyllead with permanganate in acetone (equation 124) not only effected oxidation of the hydroxymethyl group to carboxyl, but in addition one phenyl group was cleaved and replaced by hydroxyl, giving (*o*-carboxyphenyl)diphenyllead hydroxide. Upon reaction with hydrogen chloride, the hydroxide formed (*o*-carboxyphenyl)diphenyllead chloride which was con-



(123)



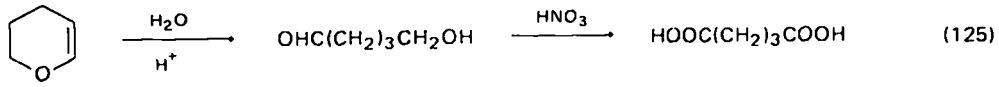


(124)

verted to its methyl ester by reaction with diazomethane. No pure product was isolated from similar oxidation attempts of the *m*-hydroxymethyl compound.

f. With oxides of nitrogen. The most common oxide of nitrogen used to convert alcohols to carboxylic acid is nitric acid. This reagent has been used to prepare substituted carboxylic acids from substituted alcohol starting materials in good yields; for example, β-chloropropionic acid in 78–79% yield from trimethylene chlorohydrin[337], and 6-bromohexanoic acid in 80% yield from 6-bromo-1-hexanol[338].

Nitric acid has also been used to prepare various dicarboxylic acids from a variety of starting materials. Glycols containing 5–9 carbons have been oxidized with 57% nitric acid at 95–105°C to give 40–50% yields of the corresponding dicarboxylic acids[339]. Treatment of cyclohexanol with 50% nitric acid afforded a 58–60% yield of adipic acid[340], while acid hydrolysis of dihydropyran followed by nitric acid oxidation of the resulting aldehyde gave a 70–75% yield of glutaric acid (equation 125)[341].



(125)

The only other oxide of nitrogen which has been used extensively for the oxidation of alcohols to acids has been dinitrogen tetraoxide. This reagent has been used at low temperatures to prepare[342] good yields of mono- and dicarboxylic acids from a variety of alcohols and glycols (Table 1).

g. With other oxides of metals. Aside from the metal oxides already discussed above, several other metal oxides have been found to be useful for both specific and general oxidation of alcohols to carboxylic acids.

The use of nickel peroxide[343,344] in the oxidation of organic compounds has recently been reviewed[345] and the reader is referred to this work for specific examples of the use of this reagent.

TABLE 1. Preparation of carboxylic acids from alcohols and glycols using nitrogen tetraoxide

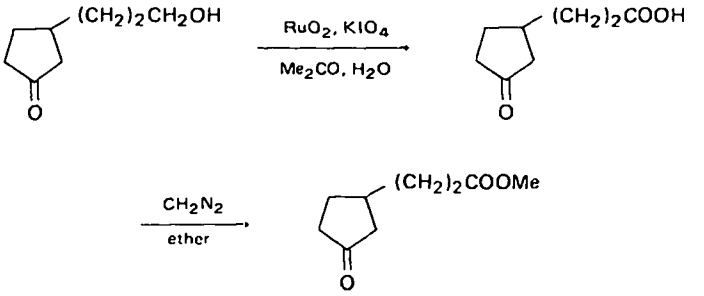
Starting material	Product	Yield (%)
$Me(CH_2)_4CH_2OH$	$Me(CH_2)_4COOH$	80
$Me(CH_2)_6CH_2OH$	$Me(CH_2)_6COOH$	83
$Me(CH_2)_8CH_2OH$	$Me(CH_2)_8COOH$	85
$Me(CH_2)_{10}CH_2OH$	$Me(CH_2)_{10}COOH$	86
$Me(CH_2)_{12}CH_2OH$	$Me(CH_2)_{12}COOH$	90
$Me(CH_2)_{14}CH_2OH$	$Me(CH_2)_{14}COOH$	90
$Me(CH_2)_{16}CH_2OH$	$Me(CH_2)_{16}COOH$	95
$PhCH_2OH$	PhCOOH	19
$PhCH_2CH_2OH$	$PhCH_2COOH$	63
$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2COOH$	85
$HOCH_2CH_2CH_2CH_2OH$	$HOOCCH_2CH_2COOH$	81
$HOCH_2(CH_2)_3CH_2OH$	$HOOC(CH_2)_3COOH$	73
$HOCH_2(CH_2)_4CH_2OH$	$HOOC(CH_2)_4COOH$	96
$HOCH_2(CH_2)_5CH_2OH$	$HOOC(CH_2)_5COOH$	91

Electrolytic oxidation using silver oxide under neutral or mildly alkaline conditions has been reported[346] to afford good yields of carboxylic acids from a variety of alcohols (Table 2). The only alcohol which was reported to give no reaction upon treatment with this reagent was *p*-nitrobenzyl alcohol.

Although ruthenium tetroxide is a powerful oxidizing agent it is not commonly used to oxidize alcohols to acids. Treatment of primary alcohols with this reagent usually affords mixtures of aldehydes and acids or acids alone in low yields, as indicated by the conversion of *n*-hexyl alcohol to caproic acid in 10% yield[347]. However, sodium or potassium ruthenate has been used successfully in converting alcohols to acids. This reagent, which is normally prepared by the reaction of ruthenium dioxide with sodium or potassium metaperiodate, has been used to oxidize 3-(3-hydroxypropyl)cyclopentanone to β-(3-oxocyclopentyl)propionic acid in 60% yield (equation 126)[348]. The acid was converted to methyl β-(3-oxocyclopentyl)propionate upon reaction with diazomethane. Other successful conversions[349] have included: benzyl alcohol to benzoic acid in 97% yield, cinnamyl alcohol to cinnamic acid in 70% yield and, cinnamic acid into benzoic acid in 91% yield.

TABLE 2. Preparation of carboxylic acids from alcohols via electrolytic oxidation

Starting alcohol	Acid product	Yield (%)
Ethanol	Acetic acid	100
n-Propanol	Propionic acid	100
1-Butanol	*n*-Butyric acid	99
2-Ethylbutanol-1	2-Ethylbutanoic acid	33
1-Pentanol	*n*-Pentanoic acid	100
3-Methylpentanol-1	3-Methylpentanoic acid	100
1-Hexanol	*n*-Hexanoic acid	35
2-Ethylhexanol	2-Ethylhexanoic acid	100
1-Octanol	*n*-Octanoic acid	22
Benzyl alcohol	Benzoic acid	60



(126)

h. With air, oxygen and/or peroxides. The effective use of air as an oxidizing agent to effect conversion of alcohols to acids is illustrated by the formation of a 96% yield[350] of lauric acid from the reaction of dodecyl alcohol with platinum oxide and air, while many examples of the usefulness of hydrogen peroxide to effect similar conversions may be found in the review by Wallace[351].

Oxygen, alone and in the presence of a variety of catalysts, has been reported to effect conversion of alcohols to acids. At 100–180°C and in the presence of chloroacetic acid or some other strong acid, atmospheric oxygen has been used[352] to convert acetates of aliphatic alcohols to bifunctional aliphatic carboxylic acids, probably via the intermediate alcohols. In the presence of platinum on charcoal[353], sodium bicarbonate and water, pentaerythritol[354] and l-sorbase[355] have been converted by oxygen to trimethylolacetic and 2-keto-l-gulonic acid in 50% and 62% yields, respectively.

Cobalt(II) salts have also been found to be effective catalysts for the oxygen oxidation of glycols to diacids. Treatment of *trans*-1,2-dihydroxycyclohexane with oxygen in benzonitrile, at 100°C in the presence of cobalt(II) acetate, affords[356] adipic and succinic acids via the intermediate dialdehydes which may also be isolated. Under similar conditions 1,2-dihydroxy-*n*-decane is converted in 70% yield into pelargonic acid (equation 127)[356]. Esters[357] may also be produced during this reaction as shown by the oxidation of 1-hexanol in the presence of cobalt(II) acetate and cobalt(II) bromide in acetic acid which gives *n*-hexyl *n*-hexanoate.

$$C_8H_{17}CH(OH)CH_2OH \xrightarrow[Co(II)]{O_2,\ PhCN} C_8H_{17}COOH \qquad (127)$$

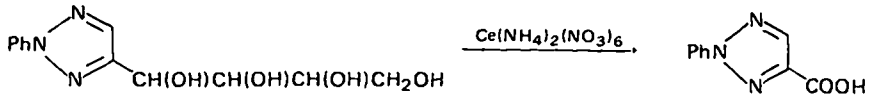
The use of catalytic quantities of Co(II) and Fe(III) have been found[358] to be necessary for the oxidation of phenol to *cis,cis*-muconic acid using peracetic acid, while the use of ammonium vanadate catalyses the oxidation of *p*-hydroxymethylbenzoic acid, *p*-(1-hydroxy-1-methylethyl)benzoic acid and *p*-di(1-hydroxy-

TABLE 3. Preparation of carboxylic acids from benzoins using ceric ammonium nitrate

Benzoin	Product	Yield (%)
Benzoin	Benzoic acid	86
4,4'-Dimethylbenzoin	4-Methylbenzoic acid	86
4,4'-Dimethoxybenzoin	Anisic acid	88
α-Naphthoin	1-Naphthoic acid	84
Furoin	2-Furoic acid	83

1-methylethyl)benzene, all to terephthalic acid[359] in the presence of aqueous hydrogen peroxide–hydrogen bromide mixtures.

i. With miscellaneous reagents. Although ceric ion normally oxidizes alcohols to aldehydes, special alcohols such as benzoins[360] are split into an aryl aldehyde and an aroyl radical upon treatment with ceric ammonium nitrate, and the radical formed is rapidly oxidized further to an arenecarboxylic acid (Table 3). Polyhydric alcohols, such as glucose phenylosotriazole, are also oxidized by ceric ion to acids, such as 2-phenyl-1,2,3-triazole-4-carboxylic acid (equation 128)[361].

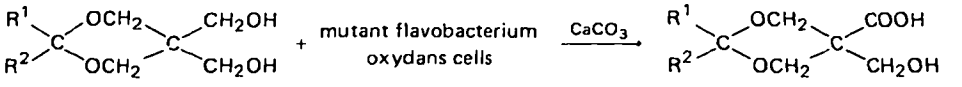


(128)

Three rather interesting reagents have been used to oxidize various alcohols to the corresponding carboxylic acids. Cold, alkaline triphenyltetrazolium chloride has been found[362] to effect an 80% conversion of Corterolone (Reichstein's compound S) to the hydroxy acid shown in equation (129), while xenic acid in water has been found[363] to be effective in oxidizing certain *vic*-diols and primary alcohols to their corresponding carboxylic acids.

(129)

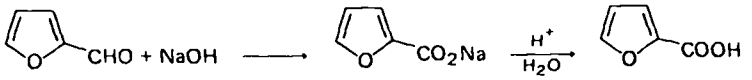
Mutant flavobacterium oxydans cells in the presence of calcium carbonate have been observed[364] to be an effective oxidizing agent for the conversion of disubstituted bis(hydroxymethyl)-1,3-dioxanes in 78–91% yields into disubstituted carboxyl hydroxymethyl-1,3-dioxanes (equation 130).



(130)

2. Oxidation of aldehydes

a. With base. The most common base-catalysed oxidation of aldehydes to carboxylic acids involves the reaction of aldehydes containing no α-hydrogen atoms with alkali, producing a primary alcohol and the salt of the corresponding acid. This reaction, known as the Cannizzaro reaction was reviewed[365] in 1944. One example is the conversion of furfural to 2-furoic acid in 60–63% yield (equation 131)[366]. Recently, the yield of this conversion has reportedly[367] been increased to 72–76%.



(131)

Passage of gaseous propanal, in a stream of nitrogen, over calcium hydroxide and zinc oxide at 450–470°C also gives rise to a Cannizzaro reaction[368] affording an 80% yield of pentan-3-one. This product is formed from condensation of the primary reaction products, propanol and propanoic acid, at these temperatures.

A modification of the Cannizzaro reaction discovered by Claisen[369] and later extended by Tishchenko[370] involves the use of sodium or aluminium alkoxides to convert both aliphatic and aromatic aldehydes into esters[371–374]. An example of this Tishchenko reaction is the conversion[375] of benzaldehyde in 90–93% yield to benzyl benzoate using sodium benzoxylate (equation 132). Nord and coworkers[376]

$$PhCHO + PhCH_2ONa \longrightarrow PhCOOCH_2Ph \qquad (132)$$

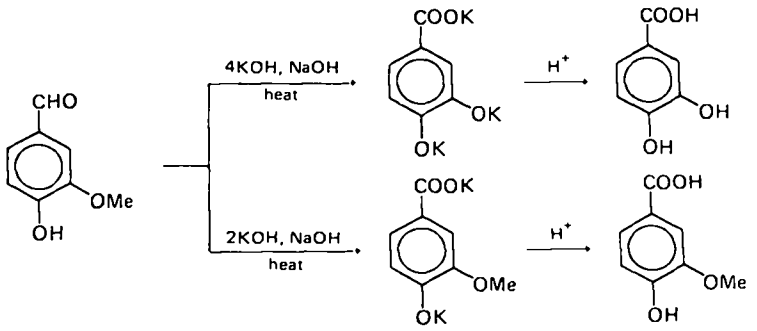
later investigated the use of magnesium aluminium complexes of the general formula $Mg[Al(OR)_4]_2$ as catalysts for this reaction, and found that in the presence of these reagents aldehydes of the type, RCH_2CHO, condense not only to afford simple esters, as with the sodium and aluminium alkoxides, but also to afford 'trimeric' esters (equation 133). In a still later study Villani and Nord[377],

$$RCH_2CHO + Mg[Al(OR)_4]_2 \longrightarrow RCH_2COOCH_2CH_2R + RCH_2CH(OH)CHRCH_2OOCCH_2R \qquad (133)$$

studied the use of various alkoxides with three aldehydes, butyraldehyde, octaldehyde and α-ethylbutyraldehyde. The yields of simple ester and glycol ester obtained for each of these aldehydes with each of the various metallic ethoxides used are recorded in Table 4. This study also revealed that aldehydes other than aliphatic ones having the α-CH_2 grouping do not afford appreciable yields of glycol esters with magnesium aluminium ethoxide and give zero yields of glycol esters with aluminium ethoxide. Stapp[378] has recently reported that boric acid but not *n*-butyl borate, acetic acid, or *p*-toluenesulphonic acid, could be used to effect a Tishchenko-type reaction as shown in equation (134). The reaction also failed when acrolein, furfural and crotonaldehyde were used.

$$RCHO + H_3BO_3 \xrightarrow[\text{cyclohexane}]{\text{heptane or}}_{250°C} RCOOCH_2R \qquad (134)$$

Examples of base-catalysed conversions of aldehydes to carboxylic acids other than via the Cannizzaro and Tishchenko reaction also have been reported. Pearl has reported the conversion of vanillin to protocatechuic acid[379] in 89–99% yield and to vanillic acid[380] in 89–95% yield by caustic alkali fusion followed by acidification of the resulting potassium salts (equation 135). The base-catalysed



(135)

TABLE 4. Reaction of aldehydes with various metallic ethoxides

	Yields of simple esters and glycols (%) using					
	Butyraldehyde		Octaldehyde		α-Ethylbutyraldehyde	
Catalyst	Butyl butyrate	Monobutyrate of 2-ethyl-1,3-hexanediol[a]	Octyl octylate	Monooctylate of 2-hexyl-1,3-decanediol[a]	α-Ethylbutyl α-ethylbutyrate	Mono-α-ethyl butyrate of 2,2,4-triethyl-1,3-hexanediol[a]
$Al(OEt)_3$	81.6	0	69.1	0	70	0
$Mg[Al(OEt)_4]_2$	26.4	44.4	19.6	42.5	54	6
$Ca[Al(OEt)_4]_2$	14.6	22.9	12.0	20.5	–	–
$Na_2Mg(OEt)_4$	3.1	41.1	–	–	–	–
$Mg(OEt)_2$	7.1	32.1	3.2	28.0	–	–
$Ca(OEt)_2$	6.8	50.3	13.1	40.4	51	4.3
NaOEt	0[b]	0	0[c]	0	–	34.3

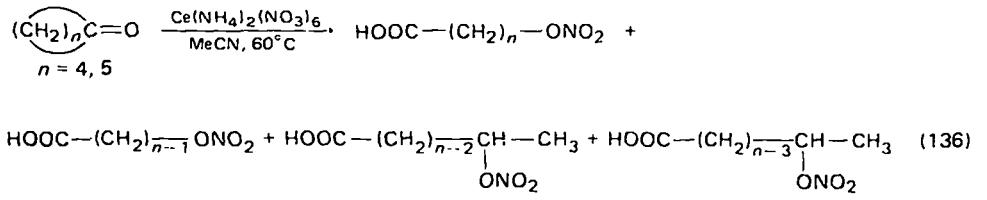
[a] The primary hydroxyl group of the diol is esterified.

[b] 88.5% of dehydrated aldol, α-ethyl-β-propylacrolein was obtained.

[c] 79.1% of dehydrated aldol, α-hexyl-β-heptylacrolein was obtained.

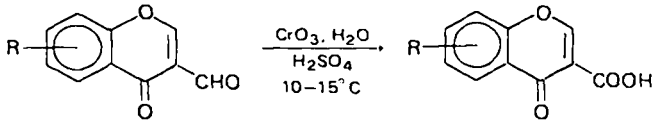
oxidation of 2-ethyl-1-hexanal to 2-ethyl-1-hexanoic acid has also been reported[381].

b. With ceric ion. The use of ceric ion for the oxidative conversion of aldehydes to the corresponding acids has been recently reviewed by Ho[382]. Using ceric ion, formaldehyde[383] and acetaldehyde[384] have been oxidized to formic acid, while cyclopentanone, cyclohexanone and norbornanone afford[385] nitrato carboxylic acids upon treatment with ceric ammonium nitrate in aqueous acetonitrile at 60°C (equation 136).



(136)

c. With oxides of chromium. Jones' reagent, chromium trioxide, water and sulphuric acid, has been the most widely used oxidizing mixture of chromium for the conversion of aldehydes to acids. It has been used to convert 2-adamantanal to 2-adamantanecarboxylic acid[386], and parent and disubstituted chromone-3-carboxaldehydes to their corresponding chrome-3-carboxylic acids, albeit in low yields (equation 137)[387]. Better yields were realized for the conversion of *cis*-4-octene-1,8-dialdehyde to *cis*-4-octene-1,8-dioic acid[388], which was converted to its methyl ester by reaction with diazomethane or methanol and sulphuric acid, and to its *t*-butyl ester by reaction with *t*-butyl alcohol and sulphuric acid (equation 138).



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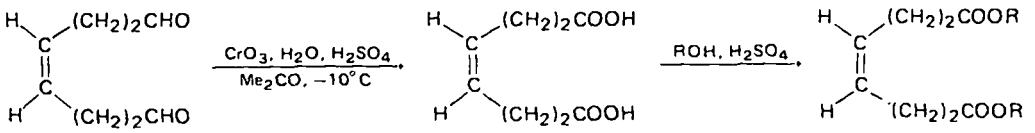

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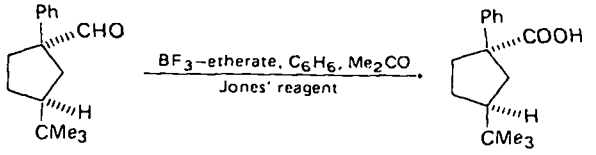
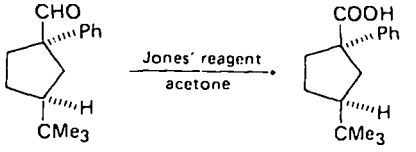


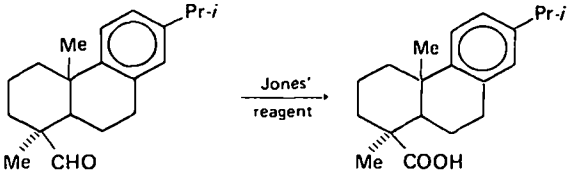
(139a)



(139b)

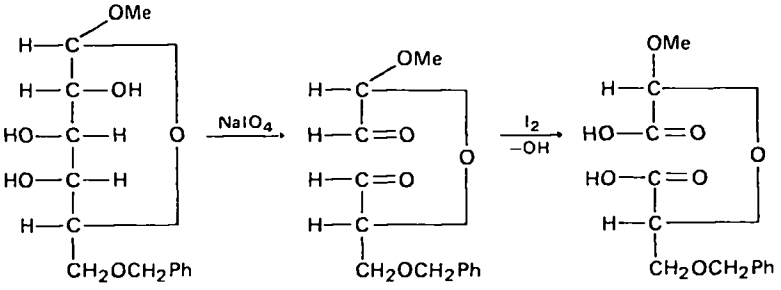
That the presence of double or triple bonds does not effect the course of reaction using Jones' reagent was demonstrated by the oxidation of *cis*-dec-2-ene-

4,6-diynal to *cis*-dec-2-ene-4,6-diynoic acid[389], while the retention of stereochemical configuration of substituents was demonstrated[390] by the conversion of 1-phenyl-*cis*- and *trans*-3-*t*-butylcyclopentanecarboxaldehyde to their corresponding 1-phenyl-*cis*- and *trans*-cyclopentanecarboxylic acids (equation 139). This stereochemical retention ability of Jones' reagent was utilized in the $C_{(4)}$ inversion of the diterpene resin acid dehydroabietic acid[391]. During the overall reaction sequence callitrisaldehyde was oxidized by Jones' reagent in 80% yield to (+)-callitrisic acid, thus allowing the inverted stereochemistry produced during the previous course of the reaction to be maintained.



(140)

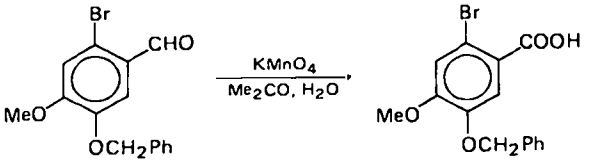
d. With periodic acid and periodates. Whereas sodium metaperiodate has been reported[392] to successfully convert 6-*O*-benzyl-α-D-galactopyranoside to its corresponding dicarboxylic acid, anomalous results have been observed[393] during the



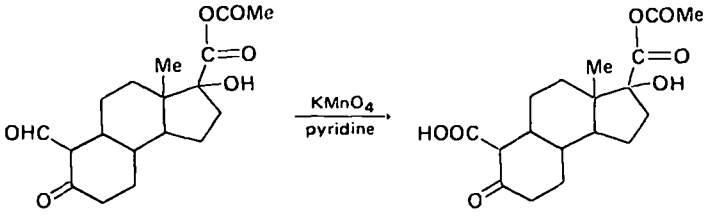
(141)

periodic acid oxidation of several α,β-unsaturated carbonyl derivatives, reductones, to α-oxoglutaric acids.

e. With oxides of manganese. Examples of the use of potassium permanganate oxidation of aldehydes to carboxylic acids in water, aqueous acetone, pyridine, acid and basic solutions have all been reported. A 1% potassium permanganate solution in water at 90–95°C has been used[394] to convert 2,3,6-trichlorobenzaldehyde to 2,3,6-trichlorobenzoic acid in 24% yield, while a more concentrated solution of potassium permanganate in aqueous acetone has been used[395] to oxidize 5-benzyloxy-2-bromo-4-methoxybenzaldehyde to 5-benzyloxy-2-bromo-4-methoxybenzoic acid in 83% yield (equation 142). Pyridine solutions of potassium permanganate have been used[396] to oxidize side-chain aldehyde groups in steroids to carboxylic acids (equation 143).

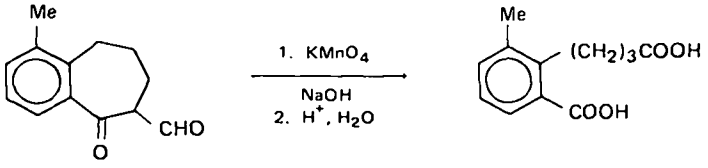


(142)



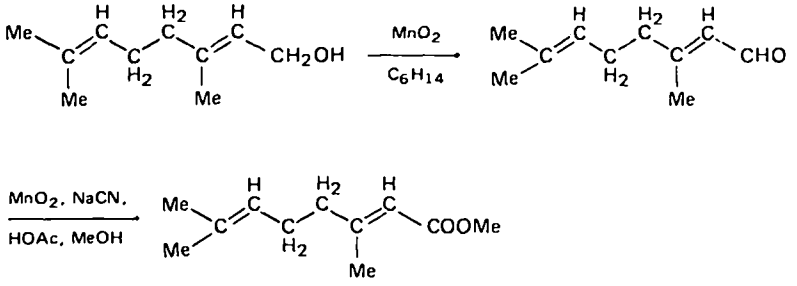
(143)

Treatment of heptanal with potassium permanganate in sulphuric acid affords[397] an 85–90% conversion to *n*-heptanoic acid while a 78–84% yield of piperonylic acid has been obtained[398] from piperonal upon treatment with alkaline potassium permanganate. Basic solutions of potassium permanganate have also been used to produce[399] γ-(2-carboxy-6-methylphenyl)butyric acid from 6-formyl-1-methylbenzosuber-5-one in 17% yield (equation 144), and 4′-fluorobiphenyl-3-carboxylic acid from 4-fluorobiphenyl-3-carboxaldehyde[400]



(144)

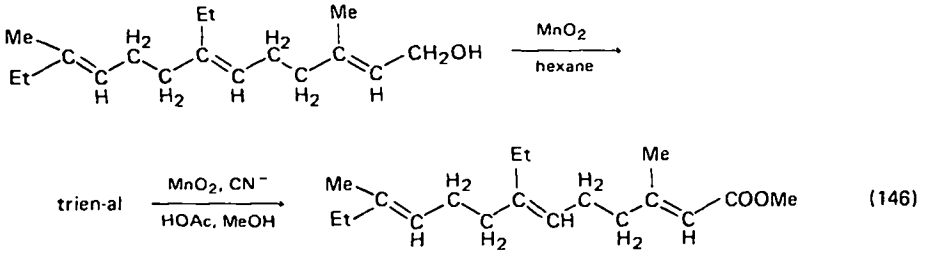
The most novel preparation of carboxylic acid esters from aldehydes using oxides of manganese is the method reported by Corey and coworkers[401]. This is a stereospecific method of converting α,β-unsaturated primary alcohols into carboxylic esters via their aldehydes. Firstly it involves the use of manganese dioxide in hexane to oxidize the alcohol to its aldehyde, and secondly the treatment of the aldehyde formed with manganese dioxide in the presence of cyanide ions in methanol to give, via suggested cyanohydrin and acyl cyanide intermediates, a conjugated carboxylic acid ester product. The conversion occurs in high yields and no *cis–trans* isomerization of the α,β-unsaturated double bonds is observed to occur. Corey[401] used this method to convert geraniol (*trans*-3,7-dimethyl-2,6-octadien-1-ol) via geranial into methyl geranate in 85–95% yield (equation 145). He also used this method[401] to convert farnesol, benzyl, cinnamyl and



(145)

furfuryl alcohols into their methyl esters in 91–95% yield. This procedure has subsequently been successfully applied to a wide variety of alcohols and aldehydes for oxidation to their corresponding carboxylic acids. van Tamelen and McCormick[402] applied this procedure to the conversion of a *trans, trans, cis*-triene alcohol (a homologue of farnesol) into its methyl ester (used in the synthesis of a

juvenile hormone) (equation 146). Other conversions utilizing this procedure for the synthesis of *Cecropia* juvenile hormones have also been reported[403,404].



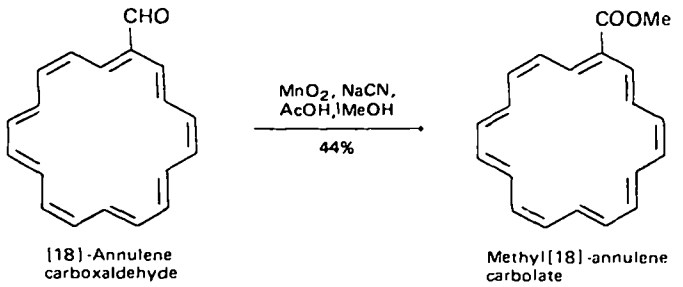
(146)

Corey's oxidation procedure has also been applied[405] to the conversion of biologically important aldehydes to their corresponding acids, and in the field of sugars to convert an unsaturated acetylated hexose[406,407] into its more unsaturated ester (equation 147). A mechanism for the conversion is proposed[406,407]. Other conversions which have been reported using this procedure are shown in equations (148)–(153).

$$\mathrm{MeCOOCH_2CH(OCOMe)CH(OCOMe)CH{=}CHCHO} \xrightarrow[\mathrm{AcOH,\ MeOH}]{\mathrm{MnO_2,\ NaCN,}} \mathrm{MeOCOOCH_2CH{=}CHCH{=}CHCOOMe} \quad (147)$$

$$\mathrm{H_2C{=}CHCMe_2C(CHO){=}CH_2} \xrightarrow[\mathrm{AcOH,\ MeOH}]{\mathrm{MnO_2,\ NaCN,}} \mathrm{H_2C{=}CHCMe_2C(COOMe){=}CH_2} \quad \text{(Ref. 408)} \quad (148)$$

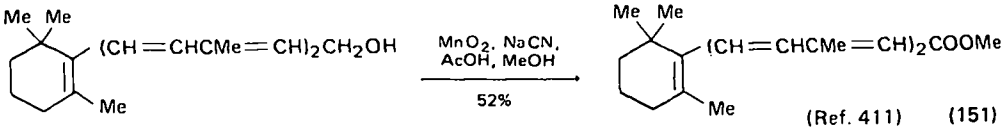
$$\underset{trans}{\mathrm{PhC{\equiv}CCH{=}CHCHO}} \xrightarrow[\mathrm{AcOH,\ MeOH}]{\mathrm{MnO_2,\ NaCN,}} \underset{trans}{\mathrm{PhC{\equiv}CCH{=}CHCOOMe}} + \mathrm{PhCH{=}C{=}CHCH_2COOMe} + \mathrm{PhCH{=}CHCH{=}CHCOOMe} \quad \text{(Ref. 409)} \quad (149)$$



(150)

[18]-Annulene carboxaldehyde

Methyl[18]-annulene carbolate



(151)

$$n\text{-}C_8H_{17}CH{=}C{=}CHCH{=}CHCHO \xrightarrow[65\%]{MnO_2,\ NaCN,\ AcOH,\ MeOH} n\text{-}C_8H_{17}CH{=}C{=}CHCH{=}CHCOOMe$$

(trans; trans)

(Ref. 412) (152)

$$n\text{-}C_5H_{11}CH{=}CHCH{=}CHCHO \xrightarrow[92\%]{MnO_2,\ NaCN,\ AcOH,\ EtOH} n\text{-}C_5H_{11}CH{=}CHCH{=}CHCOOEt$$

(trans, trans and trans, cis) (trans, trans and trans, cis)

(Ref. 413) (153)

An extensive review of the use of *Active Manganese Dioxide in Organic Chemistry* has been published in two parts[414].

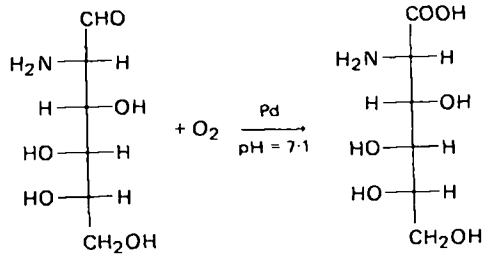
f. With oxides of nitrogen. Nitric acid in varying concentrations has been the reagent most widely used to oxidize aldehydes to carboxylic acids. 30% nitric acid at 95°C has been used[394] to oxidize 2,3,6-trichlorobenzaldehyde to 2,4,6-trichlorobenzoic acid, while 60% nitric acid under reflux for 16 hours was required[394] to oxidize 2,3,4-trichlorobenzaldehyde to 2,3,4-trichlorobenzoic acid. Fuming nitric acid was found[415] to effect a 60–65% conversion of β-chloropropionaldehyde, prepared from acrolein, to β-chloropropionic acid (equation 154).

$$CH_2{=}CHCHO \xrightarrow{HCl} ClCH_2CH_2CHO \xrightarrow{HNO_3} ClCH_2CH_2COOH \qquad (154)$$

g. With air, oxygen, acidified water and ozone. Treatment of C_4 and C_5 aldehydes in water with air at 25°C for 9 hours affords an excellent conversion[416] of the aldehydes to their corresponding acids (equation 155).

$$Me_2CHCHO + H_2O \xrightarrow[25°\,C]{air} Me_2CHCOOH \qquad (155)$$

In the presence of a variety of catalysts, oxygen has also been effective in converting various aldehydes to carboxylic acids. In the presence of a cuprous oxide–silver oxide catalyst, oxygen effected[417] an 86–90% conversion of furfural to 2-furoic acid, while in the presence of palladium at a pH of 7.1, oxygen effected[418] the conversion of an α-aminohexose into its corresponding α-amino acid in 54–60% yield (equation 156). Photochemically-induced oxygen oxidation



(156)

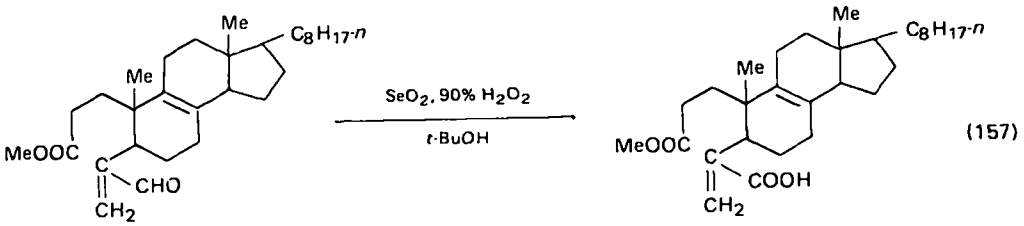
has been reported[419] to convert 19-oxo-5α-androstane-3β,17β-diacetate into its 19-carboxy derivative, when the irradiation was performed on an ethyl acetate solution of the aldehyde at 25°C for 0.5 hours.

An interesting preparation of levulinic acid in 45–69% yields involves the treatment of monomeric hexoses (4–5 h) or polymeric hexoses (6–8 h) with

hydrogen chloride–water azeotrope (20% hydrochloric acid) at 108°C and atmospheric pressure[420].

Ozone was found to be effective in oxidizing 6-formyl-1-methylbenzosuber-5-one to γ-(2-carboxy-6-methylphenyl)butyric acid, a conversion which was also accomplished with potassium permanganate (see Section II.G.2.e)[399].

h. With oxides of selenium. The use of selenium dioxide as an oxidizing agent has been reviewed[421], and a recent example[422] of its use in the field of triterpenes is shown in equation (157). In the presence of hydrogen peroxide in alcoholic media selenium dioxide has been used to oxidize acrolein to acrylates in 15–40% yield[423]. This method has also been used in the oxidation of other aldehydes in methanol or ethanol[424].



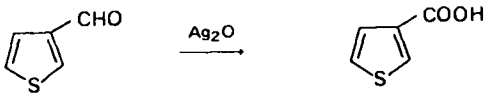
(157)

i. With oxides of silver. Several conversions of aldehydes to carboxylic acids previously reported in this review to have been accomplished with other reagents have also been reported, in most cases by the same authors, to have been effected with silver oxide. Corey and coworkers[401] reported the conversion of cinnamaldehyde, benzaldehyde and 3-cyclohexenylcarboxaldehyde to cinnamic acid (90%), benzoic acid and 3-cyclohexenylcarboxylic acid, respectively, upon treatment of the aldehydes with silver oxide and sodium or potassium cyanide in methanol. Corey also found[401] that a simple conversion of non-conjugated aldehydes to carboxylic acids could be effected by using silver oxide in tetrahydrofuran–water solutions (9:1) at 25°C under neutral conditions. Using this method and a molar ratio of silver oxide to aldehydes of 4:1, with a 14 hour reaction time, he was able to oxidize dodecanal and 3-cyclohexenylcarboxaldehyde to their corresponding acids in 90 and 97% yields, respectively. These results should be contrasted with the previous report in this review of the conversion of aldehydes to their corresponding acid esters upon cyanide-catalysed oxidation in methanol with manganese dioxide (Section II.G.2.e).

The report by Pearl[380], that vanillin was converted to vanillic acid by caustic alkali fusion also includes a prior report[425] of the same conversion being effected by silver oxide in 83–95% yield.

Conversion of callitrisaldehyde to (+)-callitrisic acid has also been accomplished[391] using silver oxide in methanol–water solution.

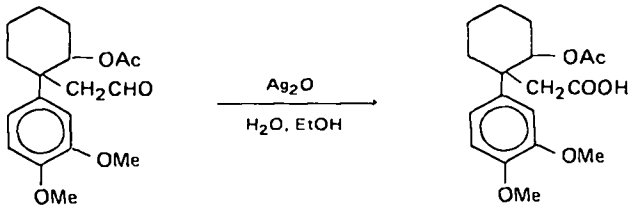
The uses of silver oxide to effect conversions of aldehydes to carboxylic acids which have not been previously reported to occur with other reagents are also reported in the literature. 5-Methylfurfuraldehyde upon treatment with silver oxide in methanol for 18 hours at 20°C affords[389] 5-methylfuroic acid, while *trans*-undec-3-ene-4,6-diynal upon treatment with silver oxide in methanol containing potassium hydroxide for 24 hours at 20°C affords[389] *trans*-dec-2-ene-4,6-diynoic acid. Two other examples of silver oxide oxidations of long-chain unsaturated aldehydes are the conversion of 6,10-dimethylundec-5,9-dienal in 55% yield[426] to its corresponding acid, and the liquid-phase oxidation, using added radical chain inhibitors, of α,β-unsaturated aldehydes[427] to their corresponding acids.



(158)

$$CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7CHO \xrightarrow{Ag_2O} CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7COOH \quad (159)$$

Silver oxide has been used as the oxidizing agent to convert 3-thenaldehyde to 3-thenoic acid in 95–97% yield (equation 158)[428], $\Delta^{9,12}$-stearadiynal to $\Delta^{9,12}$-stearadiynoic acid in 78% yield (equation 159)[429], *p*-tolualdehyde-α-D to *p*-toluic acid-α-D[430] and 2-acetoxy-1-(3,4-dimethoxyphenyl)cyclohexaneacetaldehyde to 2-acetoxy-1-(3,4-dimethoxyphenyl)cyclohexaneacetic acid (equation 160), an intermediate in the synthesis of (±)-mesembrine, in 93% yield[431].



(160)

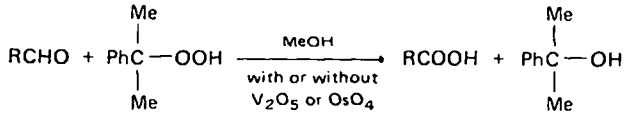
The electrolytic oxidation using silver oxide under neutral or mildly alkaline conditions previously reported[346] in this review (Section II.G.1.g) to effect good yields of carboxylic acids from alcohols has also been used to convert a variety of aldehydes to carboxylic acids as Table 5 indicates.

TABLE 5. Oxidation of aldehydes to carboxylic acids via electrolytic oxidation

Starting aldehydes	Acid product	Yield (%)
Benzaldehyde	Benzoic acid	51
Anisaldehyde	Anisic acid	57
Piperonaldehyde	Piperonylic acid	30
n-Hexaldehyde	*n*-Hexanoic acid	100
2-Ethylbutyraldehyde	2-Ethylbutyric acid	93
2-Ethylhexaldehyde	2-Ethylhexanoic acid	68
p-Nitrobenzaldehyde	*p*-Nitrobenzoic acid	38
Veratraldehyde	3,4-Dimethoxybenzoic acid	47

A comparative study of the oxidation of aldehydes to acids in aqueous base using silver oxide has been reported[432].

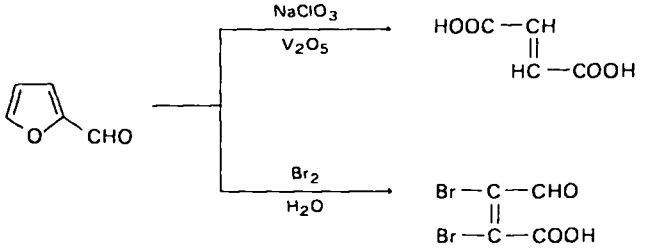
j. With miscellaneous reagents. Two metal oxides, other than those discussed thus far, which have been used to catalyse oxidation of aldehydes to carboxylic acids are osmium tetroxide and vanadium pentoxide. Both oxides have been separately used to catalyse the α,α-dimethylbenzyl hydroperoxide oxidation[433] of acetaldehyde, butyraldehyde, 2-ethylhexanal and benzaldehyde to their corresponding acids (equation 161). The oxidation has been found to occur with or without the oxides being present and the α,α-dimethylbenzyl hydroperoxide was found to be converted to 2-phenylpropan-2-ol during the reaction. Attempted oxidation of acraldehyde to acrylic acid was observed not to occur with or without



(161)

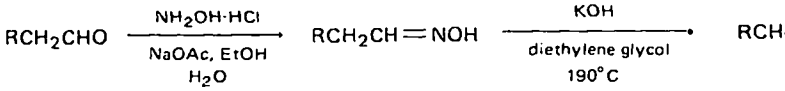
the oxides being present. *t*-Butyl hydroperoxide in the presence of metal salt catalysts, such as ferrous chloride and ferric chloride, has been used to oxidize methacrolein in methanol to methyl methacrylate[434].

Vanadium pentoxide was also found to be a useful catalyst in the sodium chlorate oxidative cleavage[435] of furfural to fumaric acid in 50–58% yield. Furfural also undergoes oxidative cleavage[436] with bromine water to give mucobromic acid (2,3-dibromo-3-formyl acrylic acid) in 75–83% yield (equation 162).



(162)

The conversion of aliphatic and aromatic aldehydes to aldoximes and their subsequent treatment with base in diethylene glycol at 170–190°C affords carboxylic acids (equation 163)[437,438]. This reaction which appears to proceed through the cyanide, which under the conditions used is then hydrolysed to the amide and finally to the acid, has been used[438] to prepare benzoic (95%), cinnamic (68%), enanthalic (63%), isobutyric (89%), phenylacetic (80%) and pivalic (38%) acids from their respective aldehydes. A reaction similar to this for the conversion of cinnamaldehyde to methyl hydrocinnamate, proceeding via its intermediate aminonitrile, has been reported[439].



(163)

An interesting reaction which demonstrates how the amount of silver ion present can effect the course of conversion of α-iodoheptanal to ethyl *n*-heptanoate has

TABLE 6. Preparation of carboxylic acids from aldehydes using Caro's acid

Aldehyde	Alcohol	Product	Yield (%)
Methacrolein	MeOH	Methyl methacrylate	90–94
Methacrolein	EtOH	Ethyl methacrylate	100
Methacrolein	*i*-PrOH	Isopropyl methacrylate	83
Acrolein	MeOH	Methyl acrylate	100
Crotonaldehyde	MeOH	Methyl crotonate	100
Propionaldehyde	MeOH	Methyl propionate	90
Benzaldehyde	MeOH	Methyl benzoate	100

TABLE 7. Preparation of carboxylic acids from aldehydes using silver(II) picolinate

Aldehyde	Acid
Butanal	Butyric acid
p-Tolualdehyde	*p*-Toluic acid
2-Ethylhexanal	2-Ethylhexanoic acid
2,3;5,6-Di-*O*-isopropylidene-α-D-mannofuranose	2,3;5,6-Di-*O*-isopropylidene mannoic acid
1,2;3,4-Di-*O*-isopropylidene-α-D-galactopyranose	1,2;3,4-Di-*O*-isopropylidene-α-D-galacturonic acid
2,3;4,5-Di-*O*-isopropylidene-D-fructopyranose	2,3;4,5-Di-*O*-isopropylidene-D-arabinohexulos-2-onic acid
2,3;4,6-Di-*O*-isopropylidene-L-sorbose	2,3;4,5-Di-*O*-isopropylidene-L-xylohexulos-2-onic acid
Benzaldehyde	Benzoic acid
2-Ethylbutanal	2-Ethylbutanoic acid
2-Furfuraldehyde	2-Furoic acid

been reported[440]. Treatment of α-iodoheptanal in ethanol–ether solution with a catalytic amount of silver ion affords ethyl *n*-heptanoate, while under the same condition with a stoichiometric amount of silver ion α-ethoxy-*n*-heptanal is the only product formed (equation 164).

$$C_5H_{11}CHICHO \begin{cases} \xrightarrow[Ag^+ \text{ (cat.)}]{EtOH,\ ether} C_5H_{11}CH_2COOEt \\ \xrightarrow[Ag^+ \text{ (stoichiom.)}]{EtOH,\ ether} C_5H_{11}CH(OEt)CHO \end{cases} \quad (164)$$

Oxidation of aldehydes with Caro's acid (peroxymonosulphuric acid), prepared by treatment of sulphuric acid with hydrogen peroxide or from $(NH_4)_2S_2O_8$, in the presence of alcohols affords the corresponding acid esters in high yields[441] as Table 6 indicates. The mechanism proposed[441] for the reaction is shown in equation (165) and is suggested to proceed via a hemiacetal peroxymonosulphate.

$$R^1CHO + R^2OH \xrightarrow{H^+} R^1CHOR^2 \xrightarrow[-H_2O]{H_2SO_5} R^1CHOR^2 \longrightarrow R^1COOR^2 + H_2SO_4 \quad (165)$$
$$\qquad\qquad\qquad\qquad\quad | \qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad OH \qquad\qquad\quad OOSO_2OH$$

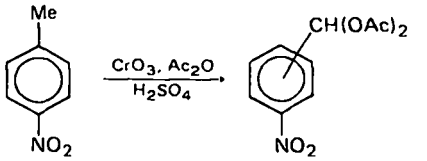
The most novel reagent which has been reported to effect oxidation of aldehydes is silver(II) picolinate[442]. Using this reagent in DMSO, a wide variety of alcohols and sugars have been effectively oxidized to their corresponding carboxylic acids as Table 7 indicates.

3. Oxidation of arenes

Since benzene di- and polycarboxylic acids, such as terephthalic acid, are of extensive industrial importance many of the reactions discussed in this section are oxidations of di- and polyalkylated benzenes which afford these acids.

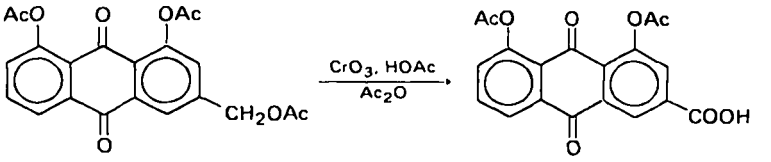
a. With oxides of chromium. Chromium trioxide in acetic acid–acetic anhydride–sulphuric acid mixtures has been used to oxidize alkyl groups on various

substituted benzenes to afford the corresponding carboxylic acid. Using this mixture of reagents, triphenyl(*p*-tolyl)silane was oxidized to *p*-(triphenylsilyl)benzoic acid[443] in 81% yield and 2-trichloroethyl-4-chlorotoluene was oxidized to 2-(β,β,β-trichloroethyl)-4-chlorobenzoic acid[444] in 93% yield, while *p*-nitrotoluene afforded a 65–66% *para* and 36–37% *ortho* mixture of nitrobenzaldiacetates (equation 166)[445].



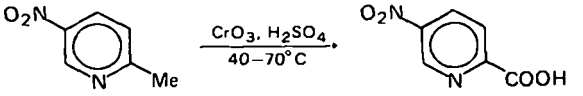
(166)

This reagent without the sulphuric acid, has been successfully applied to the oxidation of alkyl groups in more complicated systems such as steroids[446], and in aloe-emodin triacetate which was oxidized[447] to rhein diacetate (equation 167).



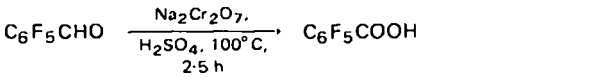
(167)

The use of chromium(VI) oxide in sulphuric acid as an oxidizing agent has also been successfully applied to alkyl side-chains of heterocyclic systems. Using this reagent mixture 3,4-dinitrotoluene was successfully[448] oxidized to 3,4-dinitrobenzoic acid, and 2-methyl-5-nitropyridine was oxidized to 5-nitropyridine-2-carboxylic acid in 80% yield (equation 168)[449].



(168)

Dichromate salts in water or sulphuric acid solutions have also found extensive use as oxidizing agents for arenes. Using sulphuric acid solution of sodium dichromate, *p*-nitrotoluene has been oxidized[450] to *p*-nitrobenzoic acid in 82–86% yield, 2,4,6-trinitrotoluene has been oxidized[451] to 2,4,6-trinitrobenzoic acid in 57–69% yield, and pentafluorobenzaldehyde has been oxidized[452] to pentafluorobenzoic acid in 75% yield (equation 169).



(169)

In water solutions sodium dichromate in an autoclave at 250°C has been used to oxidize 1,2-dimethylnaphthalene to 1,2-naphthalenedicarboxylic acid in 87–93% yield[453], and at 275°C has been used to oxidize ethyl benzene to phenylacetic acid[454]. The same mixture without the use of an autoclave has been used to oxidize acenaphthene and its chlorine, alkyl, hydroxyalkyl and sulphonic-acid substituted derivatives to the corresponding naphthalic acid derivatives[455], and 2-, 3-, 4-, 5- and 6-methylbenzo[c]phenanthrenes to their corresponding carboxy

compounds[456]. In acetic acid solution, 2-acetylfluorene has been oxidized using sodium dichromate to fluorene-2-carboxylic acid in 67–74% yield[457].

Heterocycles such as 3-picoline have been oxidized[458] to their corresponding nicotinic acids using neutral or alkaline solutions of sodium dichromate at 200–250°C.

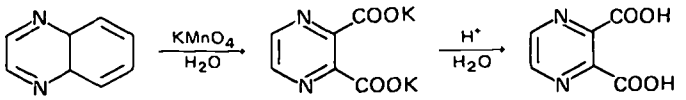
Oxidation of alkyl-substituted aromatic compounds using aqueous solutions of potassium dichromate and sodium nitrate have been reported[459] to produce the mono- and dicarboxylic acid salts of the aromatic starting material.

b. With periodic acid and periodates. Although the use of periodic acid and periodates as oxidizing agents in organic and bio-organic chemistry has been recently and thoroughly reviewed[325], one application of these reagents which should be mentioned is their use in oxidizing amines to carboxylic acids. Treatment of 3-phenyl-3-hydroxy-1-(diethylamino)propane with sodium periodate affords[460], via cleavage, 3-phenyl-3-hydroxypropanoic acid as one of the products (equation 170). Similar treatment[460] of 1-phenyl-2-piperidinoethane and 1-phenyl-2-morpholinoethane affords phenylacetic acid, also as one of their cleavage products.

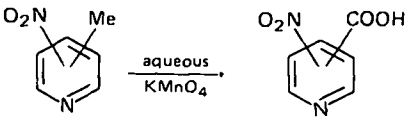
$$PhCH(OH)CH_2CH_2N(Et)_2 \xrightarrow{NaIO_4} PhCH(OH)CH_2COOH \qquad (170)$$

c. With oxides of manganese. The oxidation of arenes to carboxylic acids using potassium permanganate has been accomplished in a wide variety of solvents including water, aqueous base, acetic acid, acetone and crown ethers.

In water, potassium permanganate has been used to effect oxidation of *o*-chlorotoluene to *o*-chlorobenzoic acid in 76–78% yield[461] and quinoxaline to 2,3-pyrazinedicarboxylic acid in 75–77% yield (equation 171)[462]. Using this same mixture, α-picoline has been oxidized to picolinic acid[463], which was then treated with hydrogen chloride to produce picoline acid hydrochloride in 50–51% yield, while Brown[464,465] was able to obtain all the isomeric nitropyridine carboxylic acids from their corresponding nitropicolines (equation 172).



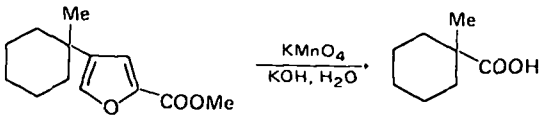
(171)



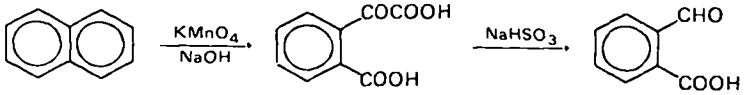
(172)

Position		Yield
NO_2	Me	(%)
3	2	45
4	2	51
5	2	30
6	2	45
2	3	42
4	3	45
5	3	40
6	3	52
2	4	37
3	4	35

In aqueous alkaline solutions, potassium permanganate has been used to oxidize methyl 4-(1-methyl-1-cyclohexyl)-2-furoate to 1-methylcyclohexanoic acid in 55% yield (equation 173)[466], *p*-tolylmercuric chloride to *p*-chloromercuribenzoic acid in 61–74% yield[467], napthalene to phthalonic acid which upon treatment with sodium bisulfide affords phthaldehydic acid in 40–41% yield (equation 174)[468],

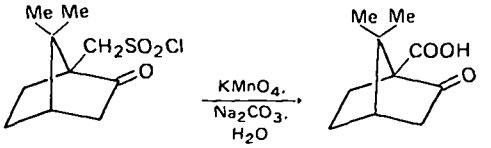


(173)



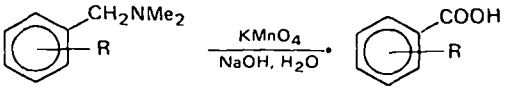
(174)

D,L-10-camphorsulphonyl chloride to D,L-ketopinic acid (2-oxo-1-apocamphanecarboxylic acid) in 38–43% yield (equation 175)[469], and 1,4-bisbromomethyl-2,3,5,6-tetrafluorobenzene to 2,3,5,6-tetrafluorophthalic acid[452].



(175)

Using sodium hydroxide solutions of potassium permanganate, Kantor and Hauser[470] converted 2,3-dimethylbenzyl alcohol and 2,3,4-trimethylbenzyl alcohol into 2,3-dimethylbenzoic acid and 2,3,4-trimethylbenzoic acid in 71 and 73% yields, respectively. With these oxidation results as models, this procedure was applied[470] to the oxidation of various substituted benzyldimethylamines to produce the corresponding substituted benzoic acids as shown in equation (176).



(176)

Starting material	Product	Yield (%)
2-Methylbenzyldimethylamine	*o*-Toluic acid	65
2,3-Dimethylbenzyldimethylamine	2,3-Dimethylbenzoic acid	75
2,3,4-Trimethylbenzyldimethylamine	2,3,4-Trimethylbenzoic acid	41
2,3,4,5-Tetramethylbenzyldimethylamine	2,3,4,5-Tetramethylbenzoic acid	37
2-Benzylbenzyldimethylamine	*o*-Benzylbenzoic acid	26

Yields of oxidized products are also reported. Application of this procedure to benzyl di(*n*-butyl)amine afforded only benzoic acid. If the amount of potassium permanganate used in the oxidation of 2,3-dimethyl-, 2,3,4-trimethyl- and 2-benzylbenzyldimethylamine was significantly increased over the amount used to obtain the products reported in the above table, then these compounds were converted[470] into 1,2,3-benzenetricarboxylic acid (hemimellitic acid), 1,2,3,4-benzenetetracarboxylic acid (prehnitic acid) and *o*-benzoylbenzoic acid in 75, 37 and 69% yields, respectively.

A kinetic study of the use of potassium permanganate in acetic acid to oxidize a variety of substituted aromatic compounds, such as toluene, ethylbenzene, *n*-propylbenzene, *i*-propylbenzene, nitrotoluene, chlorotoluene, toluic acid and the xylenes, to their corresponding carboxylic acids has been extensively investigated and reported in a series of papers by Cullis and Ladbury[471]. Although the products obtained were those expected, these studies do establish the dependence of the initial oxidation rate on the hydrogen-ion concentration, and also, that the greater part of the oxidation in these reactions is done by Mn(III) or associated ions and not by direct oxidation by the permanganate ion.

Using acetone solutions of dichromate, perfluorotetralin has been oxidized to octafluoroadipic acid[472], which was then allowed to react with aniline to form the dianilinium octafluoroadipate used as an intermediate in the preparation of di-(*S*-benzthiouranium)octafluoroadipate.

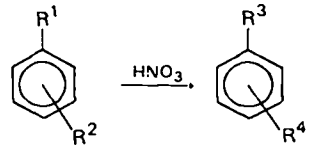
The most novel use of potassium permanganate as an oxidizing agent has been in crown ether solvents. Addition of these ethers to benzene allow up to 0.06 M of potassium permanganate to dissolve in the benzene producing the so-called 'purple benzene'. This material has been used[473] to effect the following conversions in the yields indicated; 1-heptanol to heptanoic acid (70%), benzyl alcohol to benzoic acid (100%), toluene to benzoic acid (78%) and *p*-xylene to toluic acid (100%). Another method of preparation of 'purple benzene', which affords this mixture more readily and does not require the use of the crown ethers, has been reported[474]. In this procedure quaternary ammonium ions are used to effect complete solution of the potassium permanganate in the benzene. This mixture has been used[474] to oxidize phenylacetonitrile and benzyl alcohol to benzoic acid in 86 and 92% yields, respectively, and also to oxidize 1-octanol to octanoic acid in 47% yield.

d. With oxides of nitrogen. The only oxide of nitrogen which has found extensive use in the conversion of arenes to carboxylic acids is nitric acid. In various concentrations and at various temperatures, nitric acid has been used to convert methyl, ethyl, propyl, *i*-propyl and even *t*-butyl substituents on aromatic or alicyclic rings to their corresponding carboxylic acids. In Table 8 are listed the dialkyl substituted benzenes which have been converted to their corresponding carboxylic acids using nitric acid in varying concentrations.

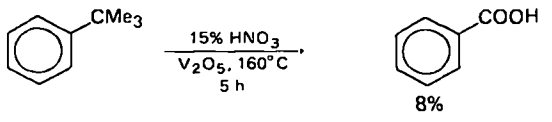
By using the results tabulated above Ferguson and Wims[478] developed a sequence for predicting the relative ease of oxidizing alkyl groups with nitric acid. They found that excluding the *t*-butyl group, the preferred oxidation of alkyl groups decreased in the order, *i*-propyl > ethyl > methyl, since this is the order of increasing electronegativity of the groups and also the order of increasing numbers of α-hydrogens. To further explore the selectivity they had proposed, they performed nitric acid oxidations on groups which have the same numbers of α-hydrogens but with varying electronegativities. Their findings showed that the relative ease of oxidation of alkyl groups, provided there is at least one α-hydrogen atom, is determined by the relative electronegativity of the alkyl group attached to the α-carbon atom. Thus, oxidation of *p*-isobutylethylbenzene afforded *p*-ethylbenzoic acid and *p*-*n*-propylethylbenzene afforded *p*-ethylbenzoic acid. Ferguson and Wims[478] further proposed that the above generalization concerning the relative ease of oxidation of carbon-attached side-chains only applied to hydrocarbon groups, and that once a carbon–oxygen, carbon–nitrogen or carbon–halogen bond was formed, the carbon attached to the ring was easily oxidized. To test this hypothesis they subjected *p*-methylbenzyl methyl ether to oxidation with 15% nitric acid and, as predicted, they obtained *p*-toluic acid as the only product.

Realizing the difficulty of oxidation of *t*-butyl substituents, Legge[480] attempted

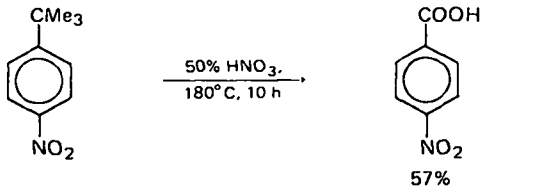
TABLE 8. Preparation of carboxylic acids from dialkylbenzenes using nitric acid



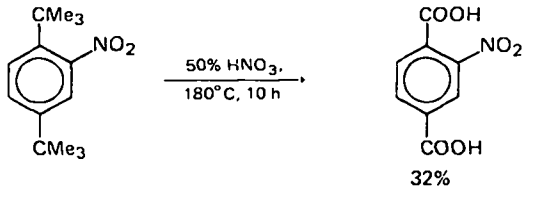
R^1	R^2	Conditions	R^3	R^4	Yield (%)	Reference
Me	*o*-Me	145–155°C, 55 h	Me	*o*-COOH	53–55	475
Me	*p*-$CHMe_2$	Reflux, 8 h	Me	*p*-COOH	51	476,478
Me	*p*-COMe	Reflux, 4 h	COOH	*p*-COOH	84–88	477
Me	*p*-Et	Reflux, 8 h	Me	*p*-COOH	–	478
Et	*p*-$CHMe_2$	Reflux, 8 h	Et	*p*-COOH	–	478
Et	*p*-(*t*-Bu)	Reflux, 8 h	*t*-Bu	*p*-COOH	–	478
$CHMe_2$	*p*-(*t*-Bu)	Reflux, 8 h	*t*-Bu	*p*-COOH	–	478
Et	*p*-(*n*-Pr)	Reflux, 8 h	Et	*p*-COOH	–	478
Et	*p*-(CH_2CHMe_2)	Reflux, 8 h	Et	*p*-COOH	–	478
Me	*p*-(*t*-Bu)	Reflux, 8 h	*t*-Bu	*p*-COOH	–	478
$CHMe_2$	*p*-(*t*-Bu)	Reflux, 11 h	*t*-Bu	*p*-COOH	66	479
$CHMe_2$	*m*-(*t*-Bu)	Reflux, 11 h	*t*-Bu	*m*-COOH	–	479
t-Bu	*p*-(*t*-Bu)	180°C, 9 h	COOH	*p*-COOH	30	480
Me	*p*-(CH_2OMe)	Reflux, 8 h	Me	*p*-COOH	–	478



(177a)



(177b)



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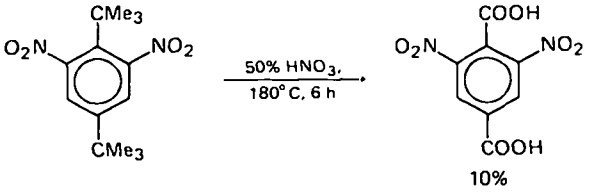


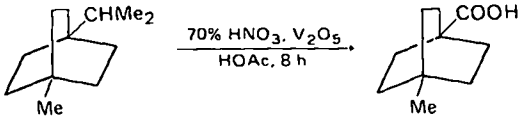
(177d)

the oxidation of *p*-di(*t*-butyl)benzene with chromium trioxide in acetic acid, aqueous potassium permanganate and 10–100% nitric acid under reflux and found that in all cases no reaction occurred. Finally, using 50% nitric acid at 180°C for nine hours he succeeded in oxidizing *p*-di(*t*-butyl)benzene to terephthalic acid in 30% yield. To establish if this procedure would be successful with more and less substituted *t*-butylbenzene derivatives he performed the reactions shown in equation (177).

Mono- and dicarboxylic acids are also obtained[481] by the acid decomposition of ω-nitrated arylnitroparaffins followed by nitric acid oxidation of the resulting aromatic monoacid. Using this procedure α-nitro-*p*-xylene was heated with concentrated hydrochloric acid in a glass pressure vessel for one hour at 150°C and afforded *p*-toluic acid which was subsequently oxidized to terephthalic acid in 96% yield by treatment with 30% nitric acid at 190°C for one hour.

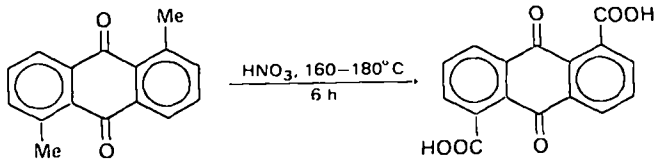
Alkylbenzenes containing multiple substituents have also been oxidized to the corresponding carboxylic acid. 4-Fluoro-2-nitrotoluene was oxidized to 4-fluoro-2-nitrobenzoic acid in 69% yield using 15% aqueous nitric acid at 190°C for five hours under pressure, while 2-bromo-4-nitrotoluene was oxidized to 2-bromo-4-nitrobenzoic acid in 76% yield[482] and 2,6-dibromo-4-nitrotoluene was oxidized to 2,6-dibromo-4-nitrobenzoic acid in 32% yield using aqueous nitric acid at 130–140°C in the presence of mercury[483].

Catalytic nitric acid oxidation has also been used to prepare bicyclic acids from bicycloalkanes. Thus, treatment of 1-isopropyl-4-methylbicyclo[2.2.2]octane with 70% nitric acid in acetic acid for eight hours in the presence of vanadium pentoxide affords[484] a 25% conversion to 4-methylbicyclo[2.2.2]octane-1-carboxylic acid (equation 178).



(178)

Nitric acid has also been used in the field of quinones to effect oxidation of 1,5-dimethylanthraquinone to anthraquinone 1,5-dicarboxylic acid in 93% yield (equation 179)[484]. This conversion was accomplished using concentrated nitric acid in a sealed tube at 160–180°C for six hours.



(179)

e. With sulphur compounds. Carboxylic acids and their derivatives can be obtained from the reaction of a variety of organic compounds with sulphur, water and a base, and with inorganic sulphates or sulphides. Sulphur, mixed with any one of a number of alkaline aqueous solutions to increase the solubility of the sulphur or the starting material in water, has been shown to be an extremely potent and selective oxidizing agent for the preparation of carboxylic acids from a variety of organic compounds as Table 9 indicates[485].

To initiate a study of the use of inorganic sulphates as oxidizing agents to effect carboxylic acid formation from a variety of products, Toland[486] investigated the

TABLE 9. Preparation of carboxylic acids using alkaline sulphur

Starting material	Base[a]	Acid product	Yield (%)[b]
m-Toluic acid	1.0 NaOH	Isophthalic	100.0
p-Toluic acid	1.0 NaOH	Terephthalic	100.0
m-Toluic acid	8.5 NaOH	Isophthalic	97.8
p-Toluic acid	8.5 NaOH	Terephthalic	97.8
p-Toluenesulphonic acid	1.0 NaOH	*p*-Sulphobenzoic +	38.5
		benzoic	29.0
m-Xylenesulphonic acid	1.0 NaOH	Isophthalic	63.6
p-Xylenesulphonic acid	1.0 NaOH	Terephthalic	46.2
Toluene	2.0 $CaCO_3$	Benzoic	61.0
m-Xylene	2.0 NaOH	Isophthalic	61.0
m-Xylene	1.3 Na_2CO_3	Isophthalic +	70.8
		benzoic	10.4
m-Xylene	2.0 $CaCO_3$	Isophthalic +	11.1
		m-toluic	12.0
m-Xylene	1.2 Na_2IP[c]	Isophthalic	33.5
m-Xylene	10 NH_4OH	Isophthalic	87.2
m-Xylene	None	Isophthalic	29.0
p-Xylene	2.0 NaOH	Terephthalic	77.0
p-Xylene	1.1 Na_2S	Terephthalic	79.0
p-Xylene	2.4 Na_2CO_3	Terephthalic	86.0
p-Xylene	8.0 $Na_2B_4O_7$	Terephthalic	76.0
p-Xylene	10 NH_4OH	Terephthalic	96.2
Acetophenone	1.0 NaOH	Benzoic	28.0
1-Butanol	4.0 NaOH	Propionic + acetic	48.0
Furan	2.0 NH_4OH	Succinic	30.0
Thiophane	4.0 NH_4OH	Succinic	19.5
Propylene	1.1 KSH	Propionic +	12.5
		acetic	7.2
Acetone	1.3 NaOH	Acetic	4.5

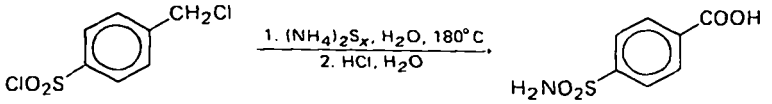
[a] Moles per mole of compound.
[b] Yields are based on the moles of stated product obtained and actual moles of starting material not recovered which could yield the product.
[c] Disodium isophthalate.

effectiveness of sulphur compounds of intermediate valences as oxidizing agents. His findings suggested that the presence of a lower valence state of sulphur was required to initiate the oxidation reaction.

To complete this study Toland then investigated the oxidative ability of various sulphates in the presence of various initiators. All the sulphates tried were found to be effective to varying degrees and the reader is referred to the original work[486] for more information. The sulphates used were: $(NH_4)_2SO_4$, $Al_2(SO_4)_3$, K_2SO_4, $KHSO_4$, $FeSO_4$ and Li_2SO_4. In a later study Toland[487] established that sulphur and water were effective in oxidizing the methylbenzenes to their respective carboxylic acids by heating the mixtures to 200–400°C under autogeneous pressures.

Inorganic sulphides have also been used to effect oxidation of aromatic alkyl side-chains to carboxylic acids. Treatment of *p*-toluic acid with sodium polysulphide, ammonium polysulphide or a sodium hydroxide–sulphur mixture affords terephthalic acid[488], while reaction of *p*-(α-chlorotoluene)sulphonic acid chloride

with ammonium polysulphide and water at 180°C for six hours affords a 48% conversion to benzoic acid sulphonamide (equation 180)[489].

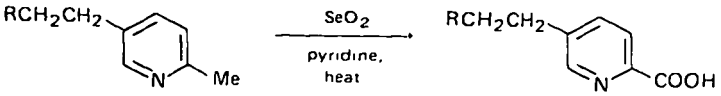


(180)

Dimerizations have also been reported during attempted oxidation of side-chain alkyl groups on aromatic molecules when sulphur compounds were used. Treatment of *m*- and *p*-toluic acids with sulphur affords the corresponding stilbenedicarboxylic acids[490], while treatment of *p*-toluic acid with several atmospheres pressure of hydrogen sulphide affords 4,4′-bibenzyldicarboxylic acid[491].

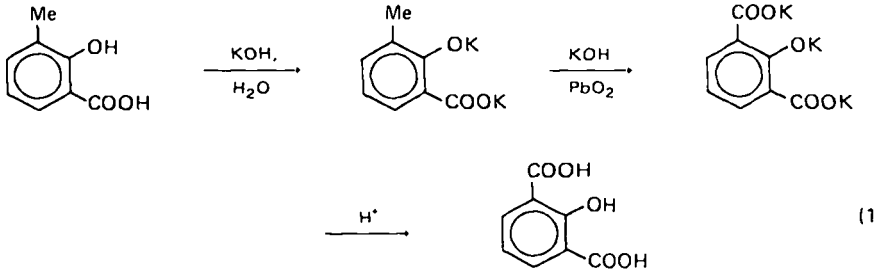
f. With oxides of selenium. Selenium dioxide alone or in combination with other reagents has been found to be moderately successful in oxidizing arenes and substituted arenes to their corresponding carboxylic acids. In the monoaromatic field, 2,3,5,6-tetrafluoroxylylene dibromide has been oxidized to 2,3,5,6-tetrafluoroterephthalic acid in modest yields using selenium dioxide[452]. In condensed ring systems 1,3,4,5,6,7,8-heptafluoro-2-methylnaphthalene was oxidized to 1,3,4,5,6,7,8-heptafluoro-2-naphthoic acid using selenium dioxide alone[472], while 2,6-dimethylnaphthalene was oxidized to 2,6-naphthalenedicarboxylic acid using selenium dioxide and nitrogen dioxide in water[492].

In the linear polyphenyl field 3-dibromomethyl-4′-fluorobiphenyl was oxidized to 4-fluorobiphenyl-3-carboxylic acid in 13% yield using selenium dioxide at 160–170°C for 10 minutes[400], while in the heterocyclic field 5-alkyl-2-picolines were oxidized to 5-alkylpyridine-2-carboxylic acids using selenium dioxide in boiling pyridine (equation 181)[493].



(181)

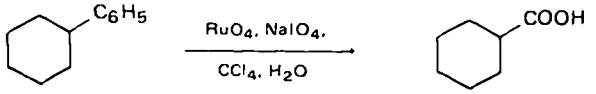
g. With other oxides of metals. Using a potassium hydroxide solution of lead dioxide, the dipotassium salt of 2-hydroxy-3-methylbenzoic acid can be oxidized to 2-hydroxyisophthalic acid in 46–61% yield (equation 182)[494].



(182)

Of the other oxides of metals used to oxidize arenes to carboxylic acids, ruthenium tetroxide has found the most extensive use. The ruthenium tetroxide used is conveniently prepared as a carbon tetrachloride solution by stirring ruthenium trichloride or ruthenium dioxide with a slight excess of sodium periodate and carbon tetrachloride overnight at room temperature. The presence of sodium periodate allows the ruthenium dioxide formed by the tetroxide substrate reaction

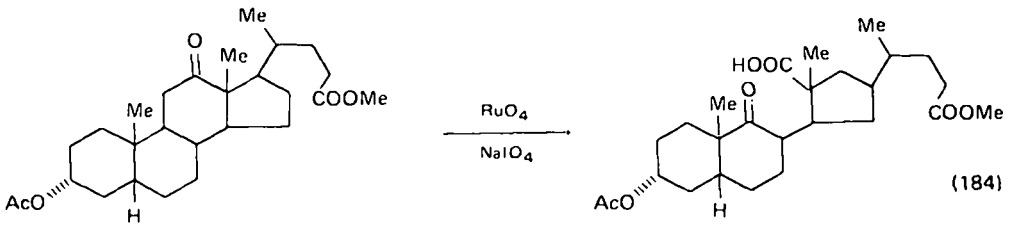
to be reoxidized to ruthenium tetroxide. Using this approach Caputo and Fuchs[495] were able to degrade benzene rings in a number of substrates, i.e. *cis*-2- and 3-phenylcyclobutanecarboxylic acids were oxidized individually to *cis*-1,2- and 1,3-cyclobutanedicarboxylic acid, identified as their dimethyl esters. Phenylcyclohexane, upon treatment with this reagent, was oxidized to cyclohexanecarboxylic acid (equation 183)[495], while *p*-(*t*-butyl)phenol was oxidized to pivalic acid.



(183)

In order to overcome the relative high cost and high molecular weight of the sodium metaperiodate which is the effective reagent in the above procedure, along with other drawbacks associated with the use of the above oxidation mixture, Wolfe and coworkers[496] developed a ruthenium trichloride-catalysed hypochlorite oxidation mixture. In this approach ruthenium tetroxide is still the actual oxidant, but household bleach, a readily available and inexpensive 5.25% aqueous solution of sodium hypochlorite, is the effective reagent. Preparation of the oxidation mixture[496] involves titration of a 2% aqueous ruthenium trichloride solution with 1.51 N sodium hypochlorite at 0°C until a yellow end-point is obtained. The resulting oxidation mixture is then added to a methylene chloride solution of the substrate and the mixture heated until a green-black colour develops. Using this approach, phenylcyclohexane was oxidized to cyclohexanecarboxylic acid in 25% yield in 10 days at 60°C, *p*-(*t*-butyl)phenol was oxidized to pivalic acid in 12% yield in seven days at room temperature, and the potassium salt of β-phenylpropionic acid was oxidized to succinic acid and benzoic acid in 95% and 6% yields, respectively, in three hours at room temperature.

The most effective use of ruthenium tetroxide as an oxidizing agent for arenes has been in the field of steroids. Examples of its effectiveness can be found in the reports of Caspi and coworkers[497], where using ruthenium tetroxide generated *in situ* from ruthenium dioxide and sodium periodate (with regeneration of the tetroxide from the dioxide formed using sodium periodate as above), oxidation of ring A or ring C of α,β-unsaturated steroids could be achieved. Thus, treatment with ruthenium tetroxide–sodium periodate mixtures oxidized testosterone to 17β-hydroxy-3,5-seco-4-nor-5-oxoanchostan-3-oic acid in 80% yield, 17β-acetoxy-3-oxo-3α-androst-1-ene to 17β-hydroxy-1,3-seco-2-nor-5α-androstane-1,3-dioic acid, 3β-acetoxy-5β-pregnan-16-en-20-one to 3β-hydroxy-17,20-dioxo-16,17-seco-5β-androstan-16-oic acid in 85% yield, and the ketone in equation (184) to methyl 3α-acetoxy-12-carboxy-9,12-seco-11-nor-9-oxo-5β-cholan-24-oate in 80% yield. Other significant oxidations are also reported[497].



(184)

h. With air, oxygen, peroxide and/or ozone. Very few oxidation reactions using oxygen as the oxidizing agent can be performed on a substrate without the

use of a catalyst. One such reaction is the oxidation of pentafluorobenzaldehyde to pentafluorobenzoic acid in 79% yield using a fine stream of oxygen bubbled through the aldehyde at 110°C for 20 hours[452].

A typical oxidation using oxygen, but employing a solvent-system catalyst, is the conversion of hexadecane in a propionic acid–acetic acid solution to a mixture of C_5 through C_{16} acids in 62% yield[498], using gases containing 14 volume % oxygen at 250 p.s.i. for five hours at 114–119°C.

Aqueous alkali solutions of oxygen have found extensive use as oxidizing agents for arenes, converting them to their corresponding carboxylic acids. Treatment of 1,6- or 2,6-dimethylnaphthalene with 7.5% sodium hydroxide aqueous solution at 260°C for one hour under oxygen pressure afforded naphthalenecarboxylic acid, phthalic acid and 1,2,4-benzenetricarboxylic acid[499], while treatment of 2,3-dimethylnaphthalene under the same conditions afforded the same three products reported above plus 1,2,4,5-benzenetetracarboxylic acid[499]. Aqueous alkali solutions of oxygen in the presence of catalysts have also been used to oxidize *o*-, *m*- and *p*-toluic acids into their corresponding dicarboxylic acids. In an expanded study Emerson and coworkers[500] found that a variety of catalysts could be used to oxidize *o*-, *m*- and *p*-toluic acids in a gas-agitated autoclave, at 260–275°C with aqueous sodium hydroxide and 1000 p.s.i. oxygen pressure for six hours. The catalysts used along with the yields obtained are shown in Table 10 for the oxidation of *p*-toluic acid to terephthalic acid. Emerson[500] also found that whereas the aluminium oxide component of the catalyst giving the highest yield could be replaced by oxides of zinc, cerium, titanium, zirconium or germanium with very little decrease in catalytic activity, replacement of the ferric oxide component with the oxides of cobalt, copper, manganese, nickel or lead afforded lower conversions. It was also found[500] that although air could be used in place of oxygen lower yields were obtained and similar lower yields were observed when potassium hydroxide–potassium carbonate was used in place of sodium hydroxide.

TABLE 10. Catalysts used for the oxidation of *p*-toluic acid to terephthalic acid, together with the yields obtained

Catalyst	Yield (%)
No catalyst	33
KVO_3	56–58
Fe_2O_3	55
$KMnO_4$	46
SeO_2	46
PbO_2	55
$K_2Cr_2O_7$	50
Fe_2O_3–Al_2O_3	66

Oxidation of the side-chains of alkyl or haloalkyl aromatics to aromatic acids was found[501] to be catalysed by a bromide in the form of hydrogen bromide[359], inorganic or organic bromides in the liquid phase with oxygen, air or hydrogen peroxide. Using this approach, *o*-, *m*- and *p*-toluic acids, *p*-hydroxybenzoic acid, *p*-xylene, *p*-diethylbenzene, *p*-nitrotoluene, *p*-methylbenzenesulphonic acid, γ-picoline, toluene, ethylbenzene, isopropylbenzene, cumic acid, α-hydroxycumic

TABLE 11. Oxidation of alkylbenzenes to carboxylic acids using cobalt(II) salts

Starting material	Catalyst	Acid product	Yield (%)	Reference
p-Xylene	$Co(OAc)_2 \cdot 4H_2O$ + HCl	Terephthalic	93	182
p-Toluic acid	$Co(OAc)_2 \cdot 4H_2O$ + HCl	Terephthalic	94	182
p-Xylene	$Co(OAc)_2 \cdot 4H_2O$ + NaBr	Terephthalic	94	182
p-*t*-Butyltoluene	$Co(OAc)_2 \cdot 4H_2O$ + NH_4Br	*p*-*t*-Butylbenzoic	95	183
p-*t*-Butylbenzene	$Co(OAc)_2 \cdot 4H_2O$ + NaBr	*p*-*t*-Butylbenzoic	94	182
t-Butylbenzene	$Co(OAc)_2 \cdot 4H_2O$ + HCl	Benzoic	16	182
Alkylaromatics	Cobalt bromides	Alkylaromatic	25–70	184

acid, α,α,'-dihydroxydiisopropylbenzene *p*-diacetylbenzene, 2,6-dimethylnaphthalene, phenanthrene, mesitylene, *p*-cyanotoluene, acetophenone and α,α-dichloroxylene were all oxidized to their corresponding mono- or dicarboxylic acids using a variety of catalysts and conditions[501].

By far the most used catalyst for the oxygen-induced oxidation of alkylbenzenes has been the cobalt ion. In the form of its acetate, cobalt(III) acetate, it has been studied[502], along with manganese(III) acetate, as the catalyst in the oxygen oxidation of *p*-cymene affording *p*-isopropylbenzoic acid and *p*-acetobenzoic acid in 90 and 10% yields, respectively. Also in the form of its acetate, Co(III) was found[503] to effect a 91% conversion of *o*-bromotoluene to *o*-bromobenzoic acid, using an oxygen–hydrogen bromide–acetic acid mixture. The combination of cobalt(II) acetate and hydrochloric acid has also been shown[504] to be an effective catalyst for the oxidation of alkylbenzenes, providing a mixed solvent system consisting of chlorobenzene–acetic acid is used. Using this system yields of 92–94% were realized for the oxidation of *p*-xylene, *p*-toluic acid and *p*-*t*-butyltoluene as Table 11 indicates.

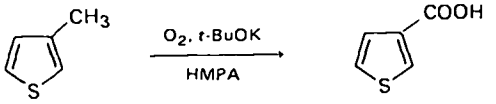
Air in the presence of a variety of catalysts has also been used[507] to oxidize arenes to carboxylic acids. Air has been used to oxidize *p*-*t*-butylbenzylbromide to *p*-*t*-butylbenzoic acid in the presence of copper nitrate[508], *p*-toluic acid to terephthalic acid in the presence of lead acetate[509] or cobalt naphthenate[510] and toluene or ethylbenzene to benzoic acid in the presence of alumina, alkaline-earth oxides, Fuller's earth or kieselguhr[511].

The autooxidation of side-chain alkyl groups to their corresponding carboxylic acids has received considerable attention since 1962. In dimethylsulphoxide-*t*-butyl alcohol–potassium butoxide mixtures, phenyl *p*-tolyl sulphone and methyl *p*-toluate have been reported[512] to undergo oxygen oxidation to phenyl *p*-carboxyphenyl sulphone and terephthalic acid, while *p*-ethyl- and *p*-isopropylbenzene, and *p*-nitro-, 2,4-dinitro- and 2,4,6-trinitrotoluene have been reported[513] to afford their corresponding carboxylic acids. In potassium *t*-butoxide–dimethylformamide solutions all three isomeric picolines have been oxidized[514] by oxygen to their corresponding carboxylic acids in the yields indicated: 2-picoline to picolinic acid in 59% yield, 3-picoline to nicotinic acid in 70% yield and 4-picoline to isonicotinic acid in 80% yield. Using potassium *t*-butoxide–diphenyl sulphoxide mixtures, toluene, *p*-nitrotoluene and *o*-xylene have been reported[515] to undergo oxygen oxidation to benzoic acid and a mixture of *o*-toluic and phthalic acid, respectively. Using potassium *t*-butoxide or potassium hydroxide in hexamethylphosphoramide, selective oxidation by oxygen of alkyl aromatics with varying side-chains to their corresponding aromatic carboxylic acid has been observed[516] to occur in the yields shown in Table 12. Employing this same system 2-methyl- and 2,5-dimethyl-

TABLE 12. Oxidation of alkylaromatics to carboxylic acids using potassium *t*-butoxide

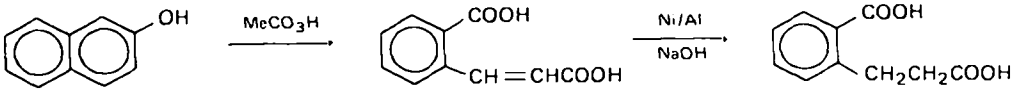
Reactant	Product acid	Yield (mole %)
Toluene	Benzoic	25–30
o-Xylene	Phthalic	35–40
m-Xylene	Isophthalic	50
p-Xylene	Terephthalic	15
Ethylbenzene	Benzoic	11
p-Cymene	*p*-Isopropylbenzoic	10
Tetralin	Phthalic	46

thiophene were converted to thiophene-2-carboxylic acid in 76 and 20% yields respectively[517], while 3-methylthiophene and toluene were oxidized to thiophene-3-carboxylic acid and benzoic acid in 19 and 50% yields respectively (equation 185).



(185)

Preparations of carboxylic acids have also been reported using peracids and hydrogen peroxide. In 40% peracetic acid β-naphthol was oxidatively cleaved to *o*-carboxycinnamic acid in 67–70% yield[518], which upon subsequent treatment with nickel–aluminium alloy (Raney catalyst) in sodium hydroxide afforded a 92–95% yield of β-(*o*-carboxyphenyl)propionic acid (*o*-carboxyhydrocinnamic acid) (equation 186). Hydrogen peroxide and heat have been found[519] to effect oxidation of the side-chain methyl group in the pyridine and quinoline palladium chloride complexes shown in equation (187) to produce the corresponding pyridine- and quinolinecarboxylic acid palladium chloride complexes, which upon treatment with acid afford the free acids. This reaction sequence has been performed on palladium chloride complexes made from 2-, 3- and 4-picoline and 2-, 3- and 4-methylquinoline.



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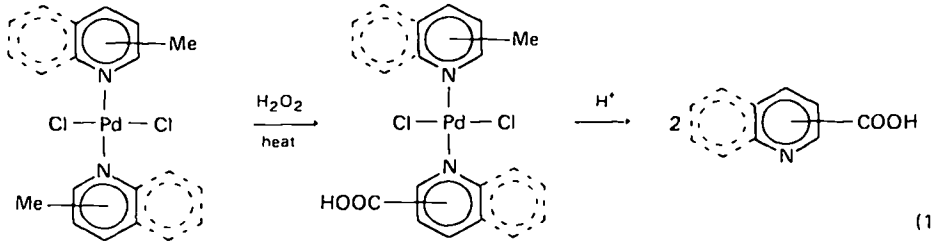
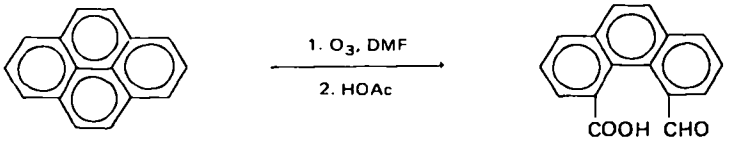


(187)

Ozone has also been found to be an effective reagent for the conversion of hydrocarbons into their corresponding carboxylic acids. In dimethylformamide, a

50% excess of ozone has been reported[520] to convert pyrene into 5-formyl-4-phenanthroic acid in 32–38% yield (equation 188). Using a mixture of ozone and air in ethyl acetate, *o*-isobornylphenol was converted[521] in 55% yield to racemic *exo*-camphane-2-carboxylic acid (equation 189), while under the same conditions,



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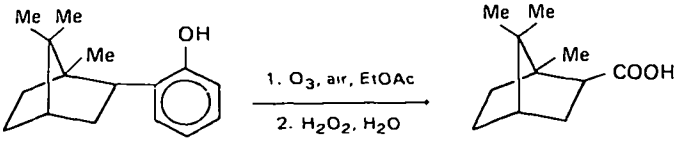
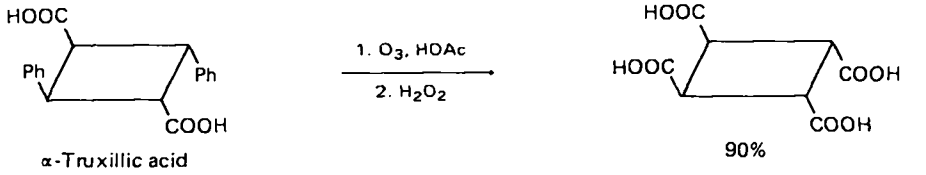


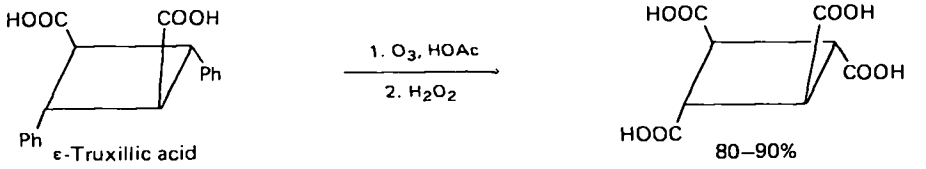
(189)

4-*exo*-isocamphenylguaiacol was converted to 2-*exo*-3,3-trimethylbicyclo[2.2.1]-heptane-6-*exo*-carboxylic acid. Application of a stream of ozone to an acetic acid solution of α-truxillic acid for 20 hours at room temperature affords a 90% conversion to 1,2,3,4-cyclobutane tetracarboxylic acid (equation 190)[522]. Similar results were obtained using ε-, γ- and *epi*-truxillic acids (equations 191 and 192), but *peri*-truxillic acid could not be oxidized under these conditions (equation 193).



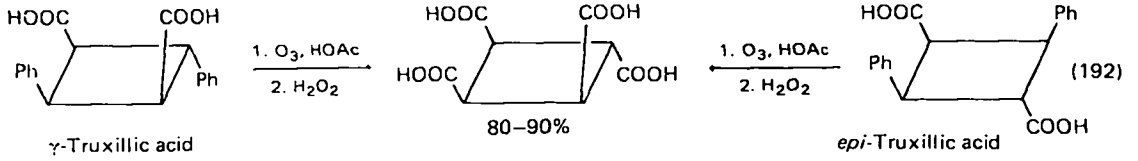
α-Truxillic acid

(190)



ε-Truxillic acid

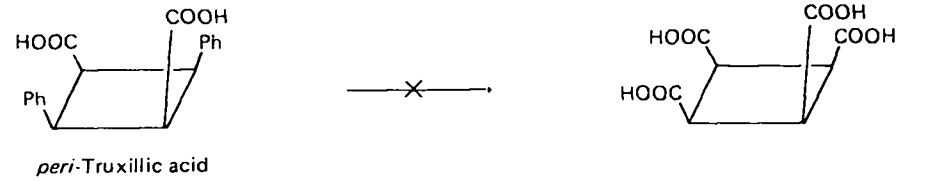
(191)



γ-Truxillic acid

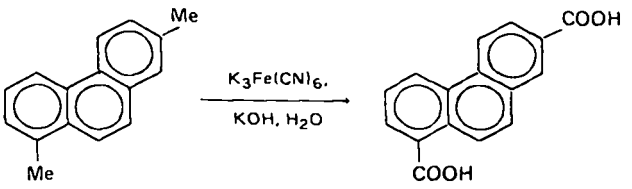
epi-Truxillic acid

(192)



peri-Truxillic acid

(193)



(194)

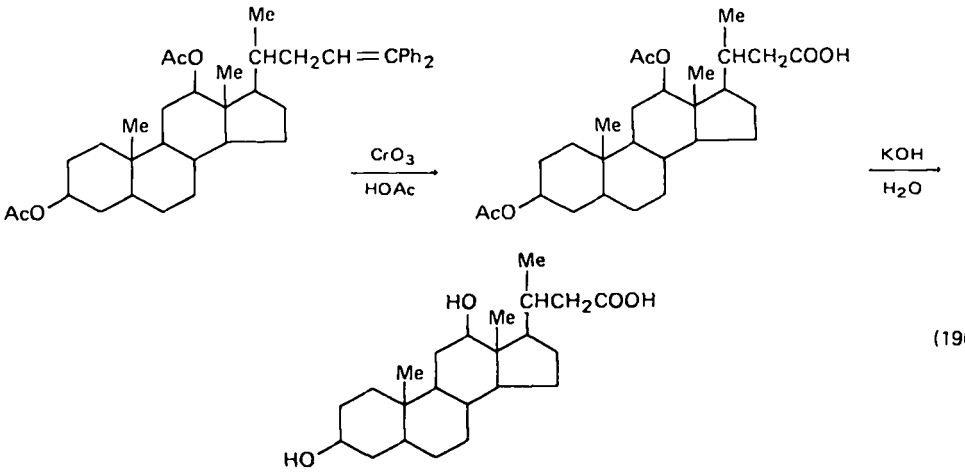
i. With miscellaneous reagents. An alkaline solution of potassium hexacyanoferrate(III) (potassium ferricyanide) has been reported[523] to successfully convert 1,7-dimethylphenanthrene to 1,7-phenanthrene dicarboxylic acid (equation 194).

4. Oxidation of double and triple bonds

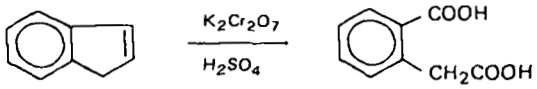
a. With base. Reactions of multiple bonds with bases which give rise to carboxylic acids and/or esters are not well represented in the recent literature. However, one example of this mode of production of carboxylic acids is the formation[524] of butanoic acid from the reaction of isobutyl 2-hexenoate with potassium hydroxide at 300–340°C (equation 195).

$$MeCH_2CH_2CH{=}CHCOOCH_2CHMe_2 \xrightarrow[300-340^\circ C]{KOH} MeCH_2CH_2COOH \qquad (195)$$

b. With oxides of chromium. Chromium trioxide in acetic acid has been used[525] to prepare dec-9-ynoic acid and dec-9-enoic acid in 60 and 63% yields respectively, from 1,1-diphenylundec-1-en-10-yne and 1,1-diphenylundec-1,10-diene. This reaction illustrates the preferred cleavage by chromium trioxide of double bonds over triple bonds when both are present. Using the same oxidizing mixture, 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene has been cleaved[527] to 3,12-diacetoxy-*nor*-cholanic acid which was not isolated but was hydrolysed with 10% aqueous potassium hydroxide to 3,12-dihydroxy-*nor*-cholanic acid in 57–68% yield (equation 196). Potassium dichromate in sulphuric acid converts indene to homophthalic acid in 66–77% yield (equation 197)[530].

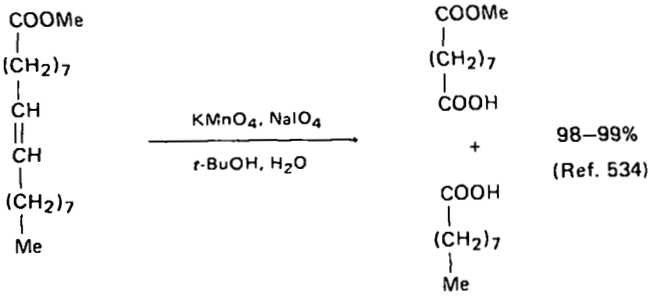


(196)



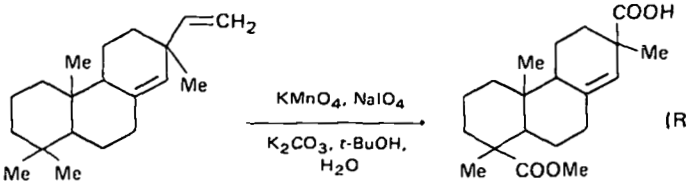
(197)

c. With Lemieux–von Rudloff reagent[325]. Although the oxidative cleavage of double bonds is not normally a useful method for obtaining carboxylic acids on a preparative scale, the use of the Lemieux–von Rudloff reagent[531-537] has proved very successful for this purpose. This mild reagent consists of aqueous sodium periodate and potassium permanganate at a pH of 7–8 and in a molar ratio of ~60:1. Studies[531-537] with this reagent have shown that the oxidation of an alkenic double bond by permanganate ion occurs via a π-complex and hypomanganate ester[308,309,538,539]. In the case of water-insoluble alkenes, good results were obtained when this oxidation mixture was used in aqueous *t*-butanol[534], pyridine[535,536] or *p*-dioxan solution[540]. The main advantages of this reagent have been found most useful in the analysis and structure determination of unsaturated fatty acids and their triglyceride derivatives (equation 198)[534,537,542-546], and in



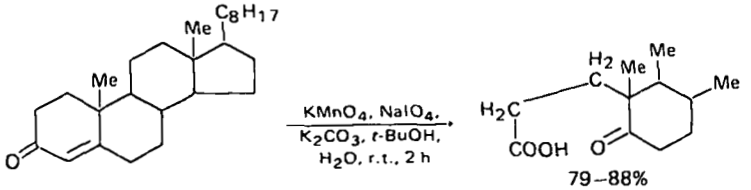
98–99% (Ref. 534) (198)

oxidative degradation of terpenes[532,533,536,547,548] and cyclic monoolefins[548,549]. The use of the permanganate–periodate reagent with monoene[550], diene and triene fatty acids[550] to optimize the oxidative cleavage has been described, as well as the non-quantitative oxidation of azelaic glycerides[551] and the unusual behaviour of some dienes (see equation 199)[552-555].



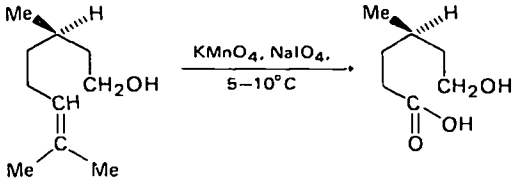
(Ref. 553) (199)

Oxidation of steroids[556] with potassium permanganate–periodate affords keto acids in excellent yields (equation 200). (*R*)-(+)-Citranello was oxidized[557] quanti-



(Ref. 556) (200)

tatively to (*R*)-(+)-6-hydroxy-4-methylhexanoic acid in an acetone–water medium (equation 201), while oxidation of a tricyclic α,β-unsaturated ketone to its corresponding keto acid was accomplished[558] in 80% yield and 15,16-dihydroxylinoleic



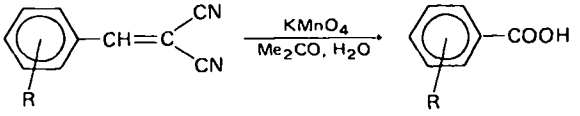
(201)

acid was oxidized to azelaic acid in good yield[559]. Evidence for the structure of the sex attractant of the gypsy moth was obtained by oxidation of (+)-10-acetoxy-*cis*-7-hexadecen-1-ol to 3-acetoxy-1-nonanoic acid in 92% yield and 7-hydroxy-1-heptylic acid, which was converted to pimelic acid in 71% yield upon treatment with alkaline permanganate (equation 202)[560]. The reagent attacked only the double bond, leaving the acetoxy and hydroxy groups unchanged.

$$\mathrm{Me(CH_2)_5CH(OAc)CH_2CH{=}CH(CH_2)_5CH_2OH} \xrightarrow{\mathrm{KMnO_4,\ NaIO_4}} \mathrm{Me(CH_2)_5CH(OAc)CH_2COOH + HOCH_2(CH_2)_5COOH} \xrightarrow{\mathrm{KMnO_4}} \mathrm{HOOC(CH_2)_5COOH} \quad (202)$$

Conversion of methyl propyl propynyl alcohol phosphate to DL-mevalonic acid 5-phosphate in 80% yield was accomplished[561,562] using the permanganate–periodate reagent, while lanosterol was oxidized to 3β-hydroxy-25,26,27-trisnorlanost-8-en-24-oic acid in 50% yield[563].

d. With oxides of manganese. Although manganese dioxide in acetic acid–acetic anhydride mixtures has been used[564] to oxidize 1-octene to a mixture of 3- and 4-decenoic acids, γ-decenolactone and 75% capric acid, and ethylene to a mixture of 20–25% γ-butyrolactone and 70–75% butyric acid, potassium permanganate is the oxide of manganese reagent of choice for oxidative cleavage of double bonds. In acetone solutions, potassium permanganate has been used to oxidatively cleave double bonds in steroids[565], and in benzalmalonitriles (equation 203)[566].



(203)

The α,β-unsaturated ester obtained from treatment of the methyl ester of mycoceranic acid (a mixture of the laevorotatory acid fraction from the lipids of tubercle bacilli) with pyridine has also been reported[567,568] to undergo double-bond cleavage upon treatment with potassium permanganate in acetone for six hours. Sodium permanganate in acetone has been reported to oxidize norbornene to *cis*-1,3-cyclopentanedicarboxylic acid in 75–95% yield[569].

Potassium permanganate in basic solutions has also been effective in producing carboxylic acids from double bonds. In aqueous acetone containing sodium bicar-

bonate, potassium permanaganate has converted 3,7-dimethyl-1-octene to 2,6-dimethylheptanoic acid in 45% yield[569], while in aqueous sodium hydroxide, potassium permanganate has converted 1-chloro-2,3,3-trifluorocyclobutene to 2,2-difluorosuccinic acid in 74–80% yield[570].

In aqueous acetone containing sulphuric acid, potassium permanganate has been used to oxidize a series of *N*-acylallylamines to *N*-acylamino acids[571], which upon acid hydrolysis afford *C*-perfluoroalkylglycines (equation 204).

$$C_nF_{2n+1}CHCH{=}CH_2 \xrightarrow[Me_2CO,\ H_2SO_4,\ r.t.]{KMnO_4,} \underset{\underset{HNCOR}{|}}{C_nF_{2n+1}CHCOOH} \xrightarrow[H_2O]{H^+} \underset{\underset{NH_2}{|}}{C_nF_{2n+1}CHCOOH} \qquad (204)$$

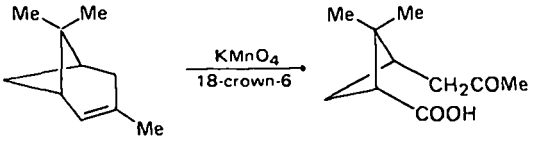
(19) (20)

n	R	% Yield 19	% Yield 20
1	$OCH_2C_6H_5$	85	57
1	C_6H_5	92	75
2	C_6H_5	82	62
3	C_6H_5	82	54

Permanganate ion in benzene and in the presence of a phase-transfer catalyst has been reported[572] to convert terminal olefins to carboxylic acids containing one carbon less than the starting material in excellent yields (equation 205). Using this same approach with the previously described 'purple benzene', α-pinene was converted in 90% yield to *cis*-pinoic acid (equation 206)[473], *trans*-stilbene in 100% yield to benzoic acid[473,474], cyclohexene in 100% yield to adipic acid[473] and 1-octene in 81% yield to heptanoic acid[474].

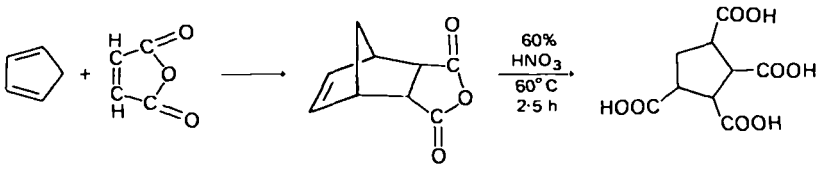
$$Me(CH_2)_5CH{=}CH_2 \xrightarrow[C_6H_6,\ Q^+]{MnO_4^-,} Me(CH_2)_5COOH \qquad (205)$$

Q^+ = phase-transfer catalyst



(206)

e. With oxides of nitrogen. Nitric acid (60%) has been used to oxidatively cleave[573] *endo-cis*-bicyclo[2.2.1]hep-5-ene-2,3-dicarboxylic anhydride, the adduct formed from reaction of cyclopentadiene with maleic anhydride, to *cis, cis cis*-1,2,3,4-cyclopentanetetracarboxylic acid in 80–85% yield (equation 207).



(207)

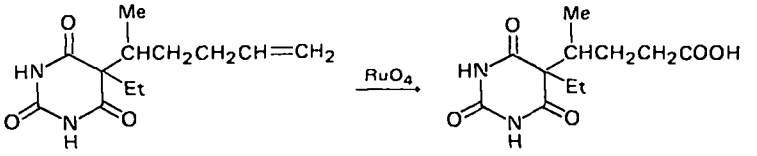
The most novel preparation of carboxylic acids and esters using an oxide of nitrogen has stemmed from the reaction of acetylenic hydrocarbons with nitrous

TABLE 13. Preparation of carboxylic acids via oxidation of acetylenes with nitrous oxide

Starting material	Conditions	Product	Yield (%)
Acetylene	EtOH, 300°C, 500 atm	Ethyl acetate	68
1-Hexyne	EtOH, 300°C, 500 atm	Ethyl hexanoate	56
1-Heptyne	MeOH, 250°C, 300 atm	Methyl heptanoate	57
1-Heptyne	MeOH, 300°C, 300 atm	Methyl heptanoate	87
Phenylacetylene	EtOH, 300°C, 500 atm	Ethyl phenylacetate	33
Phenylacetylene	H_2O, 300°C, 500 atm	Phenylacetic acid	20
5-Decyne	EtOH, 300°C, 500 atm	Ethyl 2-butylhexanoate	–
Diphenylacetylene	MeOH, 300°C, 500 atm	Methyl diphenylacetate	–

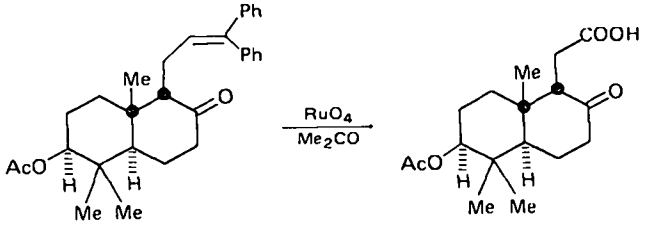
oxide at 200–300°C and 100–500 atm[574]. When this reaction is carried out in water carboxylic acids are formed, while using alcohols as solvents produces esters. The mechanism for this reaction is thought to involve initial formation of an α-diazo ketone or an α-diazo aldehyde which then loses nitrogen and undergoes anionotropic rearrangement to a ketene, which upon reaction with water or an alcohol leads to an acid or an ester. Listed in Table 13 are the acetylene starting materials and the conditions used, along with the products and yields obtained.

f. With oxides of ruthenium. Ruthenium tetroxide, prepared as previously described from the reaction of sodium metaperiodate with ruthenium chloride or ruthenium dioxide, has been used to oxidatively cleave cyclohexene to adipic acid in 86–95% yield[496], norborene to *cis*-1,3-cyclopentanedicarboxylic acid in 80–90% yield[575], and 5-ethyl-5-(1-methyl-4-pentenyl)barbituric acid to 5-ethyl-5-(1-methyl-3-carboxypropyl)barbituric acid in 81% yield (equation 208)[576].



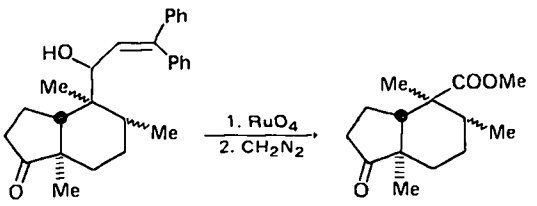
(208)

In the field of steroids, ruthenium tetroxide in aqueous acetone has been used to prepare[577] (–)-5,5-dimethyl-6-acetoxy-2-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-naphthaleneacetic acid in 89% yield from the diphenylethyleneacetoxyketone shown in equation (109). Comparable results were obtained with similar systems (equations 210 and 211)[578].

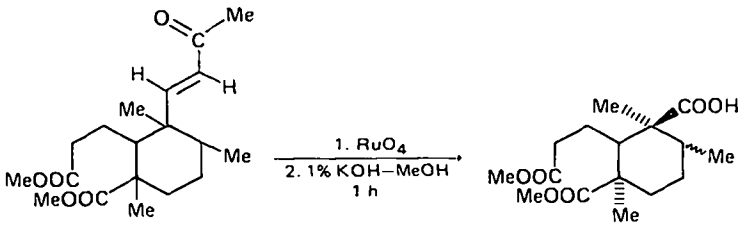


(209)

It has been reported[579] that when alkynes are treated with ruthenium tetroxide, prepared by reaction of ruthenium dioxide with sodium hypochlorite or sodium metaperiodate, in aqueous carbon tetrachloride at 0°C, a facile and rapid oxidation



(210)



(211)

occurs converting the alkyne to its corresponding α-diketone and/or carboxylic acid. Table 14 reports the results obtained[579].

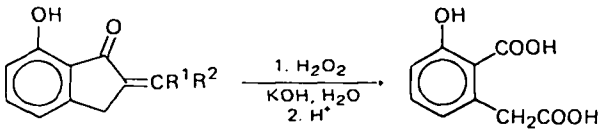
TABLE 14. Preparation of carboxylic acids via oxidation of acetylenes with ruthenium tetroxide

$$R^1C{\equiv}CR^2 \xrightarrow[CCl_4-H_2O,\ 0^\circ C]{RuO_4} R^1COCOR^2 + R^1COOH$$

Starting material	Diketone (mole %)	Acid (mole %)
$R^1 = R^2 = C_6H_5$	83.0	7.5
$R^1 = R^2 = Bu$	70.0	19.4
$R^1 = R^2 = Pr$	58.5	40.0
$R^1 = C_6H_5$, $R^2 = H$	–	66.0
$R^1 = t$-Bu, $R^2 = H$	–	60.0

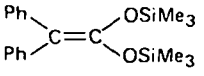
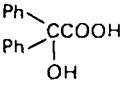
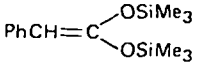
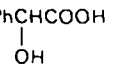
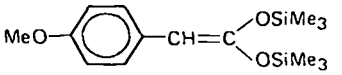
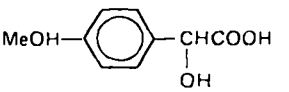
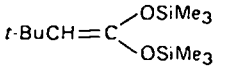
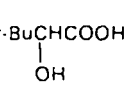
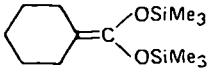
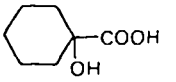
Although α-diketones can be cleaved with hypochlorite or periodate alone, under the conditions used in this investigation, all the diketones reacted too slowly to account for the amount of acid observed. It was also reported that no reaction occurred when hypochlorite alone was used[579].

g. With periodate, peroxyacids and ozone. The preparation of 3-hydroxyhomophthalic acid, a key precursor in the synthesis of 8-hydroxy-3(3′-hydroxy-4′-methoxyphenyl)dihydroisocoumarin (phylladulcin), has recently been reported[580] to have been accomplished by oxidative ring-cleavage of several substituted methylene derivatives of 7-hydroxyindan-1-one using basic hydrogen peroxide (equation 212).

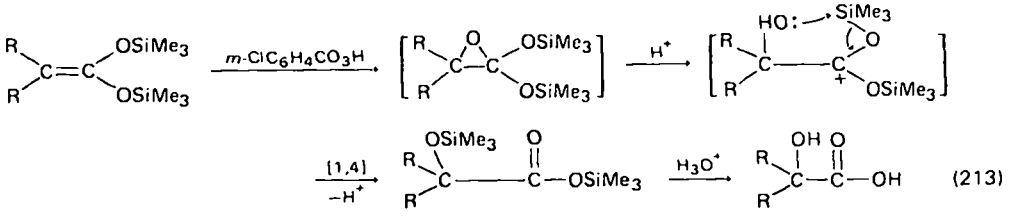


(212)

TABLE 15. Preparation of α-hydroxy carboxylic acids via oxidation of ketene bis(trimethylsilyl)acetals with *m*-chloroperbenzoic acid

Acetal	Product	Yield (%)
		81
		82
		83
		50
		80

An extremely general high-yield method for the preparation of α-hydroxy carboxylic acids has recently been reported[581] which involves oxidation of ketene bis(trimethylsilyl)acetals with *m*-chloroperbenzoic acid. The utility of this reaction is indicated in Table 15 which lists the starting acetals used and the products and yields obtained. The mechanism proposed[581] for this reaction is shown in equation (213), and involves initial preparation of an epoxide followed by ring-opening and a [1,4]-sigmatropic trimethylsilyl shift.



(213)

Although it had been previously reported that perbenzoic acid oxidation of phenylacetylene afforded phenylacetic acid[582], and that peracetic acid had no

effect on phenylacetylene[583], in a recent study[584] of peracid oxidation of phenyl- and diphenylacetylene with a methylene chloride solution of trifluoroperacetic acid containing disodium hydrogen phosphate afforded a 76% yield of benzil and a 17% yield of benzoic acid. Using the same reaction mixture with phenylacetylene afforded a 25% yield of benzoic acid and a 38% yield of phenylacetic acid, while with perbenzoic acid methyl phenylacetate (42.5%), ethyl phenylacetate (8.1%), methyl benzoate (3%), benzaldehyde (11.1%) and benzoic acid (43.5%) were obtained. Reaction of phenylacetylene with a methylene chloride solution of peracetic acid at room temperature afforded benzoic acid (23%) and phenylacetic acid (17%), but if the reaction was run using 40% peracetic acid in methylene chloride–acetic acid for 8 days a mixture consisting of 18% benzyl acetate, 39% acetylmandelic acid, 17% phenylacetic acid and 23% benzoic acid was obtained.

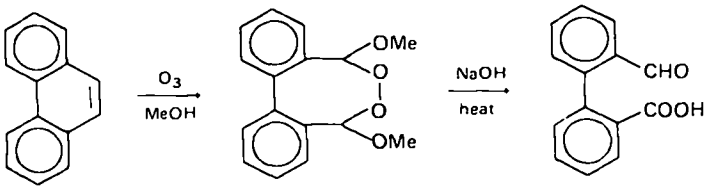
By far the premier reagent used to oxidize olefins to carboxylic acids has been ozone. At least five review articles have been published which discuss all or selected aspects of the ozonolysis reaction. In 1940 Long[585] reviewed 'The ozonization reaction', Bailey[586] in 1958 wrote on 'The reaction of ozone with organic compounds', in 1968 Murray[587] reviewed 'The mechanism of ozonolysis', Griesbaum[588] in 1969 discussed 'Carboxylic acid preparation by olefin ozonolysis', while in 1976 Dryuk[589] reviewed 'The mechanism of epoxidation of olefins by peracids'.

Ozonolysis of 2-hydroxymethylene-7-hydroxy-indan-1-one and 2-hydroxymethylene-7-phenylindan-1-one has been reported[590] to afford 3-hydroxyhomophthalic acid, while ozonolysis of norbornene affords[591–593] *cis*-1,3-cyclopentanedicarboxylic acid, both reactions occurring in good yields. On the other hand, a poor yield of only 3% was realized[594] in the preparation of 5-ethyl-5-(1-methyl-3-carboxypropyl)barbituric acid from 5-ethyl-5-(1-methyl-4-pentenyl)barbituric acid by ozonolysis.

Treatment of long-chain olefins with ozone has been reported under a variety of conditions and in the presence of a variety of catalysts. 1-Dodecene in pentane at $-10^{\circ}C$ and 1-tridecene in chloroform at $0^{\circ}C$ both afforded[595] their corresponding carboxylic acids, undecanoic and dodecanoic acid, respectively, upon treatment with ozone followed by hydrolysis. Using alcohols as solvents 1-dodecene was oxidized with ozone to undecanoic acid at -20 to $-30^{\circ}C$[596], while undec-10-ene-1-oic acid in ethanol was converted to 1,10-dodecanedioic acid in 50% yield using ozone[597].

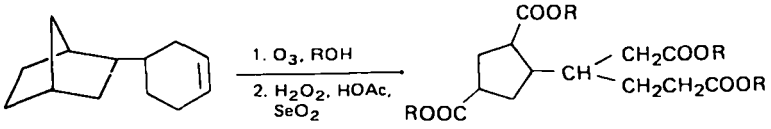
In 70% nitric acid at atmospheric pressure and in the presence of Ce(III) or Ce(IV) ions α- and β-olefins only are oxidized by ozone to carboxylic acids[598]. Branched-chain olefins are also oxidized[598] under these conditions if the branching occurs in other than the β-position for α-olefins or in the γ-position for β-olefins. Using acetic acid as the solvent stearolic acid has been oxidized by ozone to azelaic acid (1,9-nonanedioic acid) in 69–80% yield[599].

Ozone has also been used to ring-open cyclic molecules affording both mono- and dicarboxylic acids or esters. Treatment of phenanthrene with ozone in methanol affords[600] 3,8-dimethoxy-4,5,6,7-dibenzo-1,2-dioxocyclooctane which



(214)

upon sodium hydroxide hydrolysis gives diphenaldehydic acid (2′-formyl-2-biphenylcarboxylic acid) in 81–88% yield (equation 214). Ozonolysis of an ethyl bromide solution of 5-methyl-1-(2′,6′-dimethylheptyl)-1-cyclohexene or 1-dodecyl-5-methyl-1-cyclohexene followed by hydrogen peroxide–acetic acid hydrolysis of the ozonides affords 4,8,12-trimethyl-6-ketotridecanoic acid and 4-methyl-6-ketostearic acid in yields of 90% and 90–95%, respectively[569]. Reaction of cyclohexene, cyclohexenylnorbornene (equation 215), 3-methyl-4-(1-propenyl)-



(215)

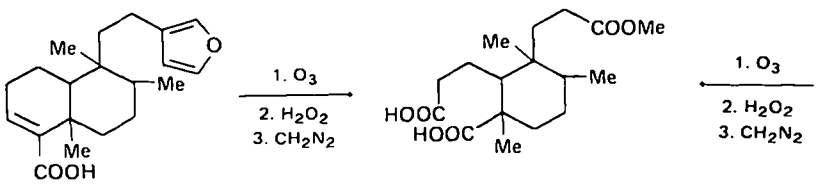
cyclohexene, 1-heptene and 4-vinylcyclohexene in methyl, *n*-butyl or *n*-octyl alcohols with ozone, followed by decomposition of the ozonides with hydrogen peroxide–acetic acid containing selenium dioxide, affords the corresponding ring-opened methyl, *n*-butyl or *n*-octyl esters in yields ranging from 35–70%[601]. Although the treatment of cyclic olefins with ozone followed by oxidation of the ozonides to the corresponding terminal diacid is the common[602-607] two-step process used by most workers for the oxidative cleavage of cyclic olefins, a novel one-step approach has been reported in which the initially formed ozonolysis products react immediately with the oxidizing reactant present. Thus, treatment[608,609] of olefins in emulsions of aqueous, alkaline hydrogen peroxide with ozone affords the α,ω-dicarboxylic acids listed in Table 16 in one step in the yields indicated. Reaction of cyclooctene in a hydrogen cyanide emulsion in water with ozone affords 2,9-dihydroxysebacic acid[609].

Ozone has also been used extensively in the field of terpenoids and steroids[610] to effect double-bond oxidative cleavage of carboxylic acids. Treatment of hardwickiic acid (21) (a constituent of the oleo-resin of *Hardwickia pinnata*) or kolavic acid (23) with ozone followed by hydrogen peroxide cleavage of the ozonide and esterification with diazomethane affords the methyl ester 22[578]. Although it has been reported[611] that treatment of 3α-hydroxy-21-benzlidenepregnan-11,20-diene-

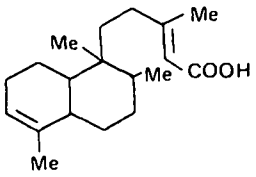
TABLE 16. Preparation of dicarboxylic acids via oxidation of olefin with hydrogen peroxide and ozone

Olefin	Carboxylic acid	Mole %
Cyclohexene	Adipic	26
Cyclooctene	Suberic	63
1,5-Cyclooctadiene	1,6-Dicarboxyhexene-3	52
1,5,9-Cyclododecatriene	1,10-Dicarboxydecadiene-3,7	60
Dicyclopentadiene[a]	2,3,5-Tricarboxycyclopentylacetic or	60
	6,8-dicarboxybicyclo[3.3.0]octene-4 and	
	1-carboxynorbornylene-2-acetic	55
Indene	Homophthalic	83
Acenaphthylene	1,8-Naphthalic	82
Norbornylene	Cyclopentanedicarboxylic-1,3	68
4-Cyclohexene-1,2-dicarboxylic anhydride	1,2,3,4-Tetracarboxybutane	73

[a] Product depends upon conditions used.

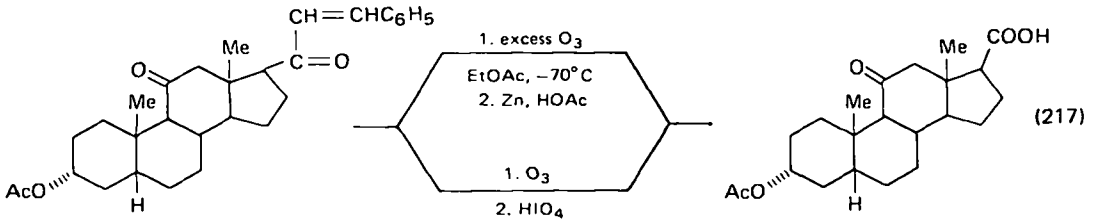


(21) (22) (216)



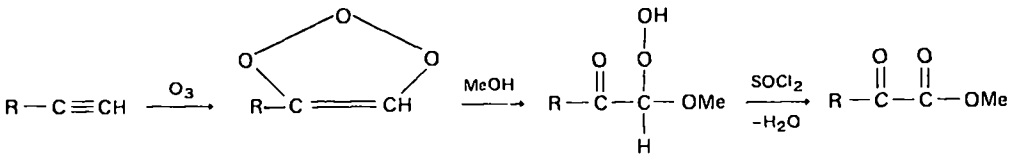
(23)

3-acetate (24) with ozone followed by periodic acid affords an 86% yield of 3α-acetoxy-11-ketoetianic acid (25), omission of the periodic acid treatment and reaction of 24 with excess ozone in ethyl acetate at −70°C, followed by treatment with zinc in acetic acid, gives the same product[612]. It was also reported[612] that ozonolysis of 3α-hydroxy-21-benzylidenepregnane-11,20-dione in ethyl acetate at −70°C followed by treatment with zinc in acetic acid affords 3,11-diketoetianic acid in 71% yield, while reaction of the dione with potassium permanganate in 85% aqueous acetone at room temperature for 15 hours affords a 62.8% yield of 3α-hydroxy-11-ketoetianic acid. In a similar manner a substituted carotenoid[613,614] was converted to 2,2-dimethylheptan-6-oneoic acid, and the acetate of 4,4a,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-4b,8,8-trimethyl-2(3*H*)-phenanthrone was converted[579] to the acetate of 1,2,3,4,4a,5,6,7,8,8a-decahydro-6-hydroxy-2-oxo-5,5,8a-trimethyl-1-naphthalenpropionic acid.



(24) (217) (25)

Reaction of ozone with triple bonds also leads to the production of carboxylic acids and esters regardless of where the triple bond is located in the molecule. Molecules containing interior triple bonds such as 5-decyne, upon treatment with ozone in carbon tetrachloride–acetic acid solutions give[615] a 35% yield of pentanoic acid, while ozone oxidation of diphenylacetylene has been reported[615,616] to yield 5–51% of benzil with the other product being benzoic acid. Ozonolysis of interior or terminal triple bonds produces acids, while the same reaction performed in alcohol solvents affords esters[617]. A novel preparation of α-keto methyl esters has been reported[618] to occur upon treatment of 1-hexyne, 1-octyne and phenyl-

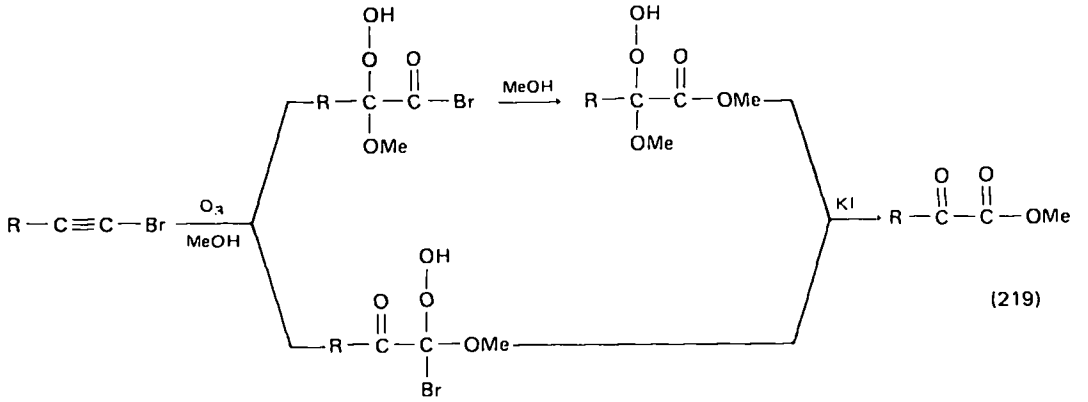


R = C_4H_9, C_6H_{13}, C_6H_5 (218)

acetylene with ozone in dry methanol, followed by dehydration of the intermediate α-hydroperoxy-α-methoxy aldehydes with thionyl chloride, as shown in equation (218). Unfortunately, this method gave the α-keto methyl esters in only 10–20% yields. However, modification of the above reaction by using 1-bromoacetylenes, which are readily available from the corresponding terminal acetylenes by treatment with alkaline aqueous solutions of sodium or potassium hypobromite[619], gave the desired α-keto methyl esters shown in Table 17 via the mechanism shown in equation (219), in the yields indicated. Ozonolysis of the 1-bromoacetylenes in methanol solution should give two peroxides both of which can be converted to α-keto esters by reduction with potassium iodide.

TABLE 17. Oxidation of 1-bromoacetylenes with alkaline sodium or potassium hypobromite

Starting material	α-Keto ester	Yield (%)
$C_4H_9C{\equiv}CBr$	$C_4H_9COCOOMe$	40
$C_6H_{13}C{\equiv}CBr$	$C_6H_{13}COCOOMe$	50
$C_6H_5C{\equiv}CBr$	$C_6H_5COCOOMe$	50



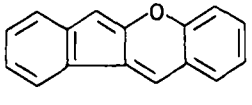
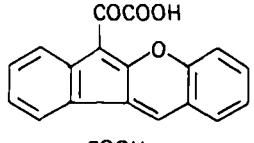
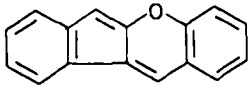
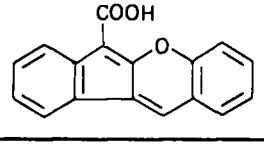
(219)

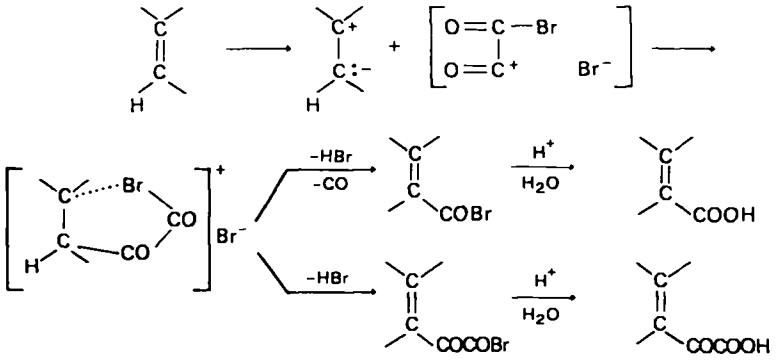
Carbohydrates containing terminal triple bonds have also been converted to carboxylic acids upon reaction with ozone in carbon tetrachloride solutions[620].

h. With miscellaneous reagents. Reaction of 11-hydroxy-10-oxoheptadecanoic acid with lead tetraacetate in 90% acetic acid for one hour affords heptanal and sebacic acid[525]. Other examples of the reaction of lead tetraacetate with triple bonds also appear in the literature[526–528].

A novel preparation[621a–d] of carboxylic acids involving the reaction of olefins with oxalyl chloride[621a–c] of oxalyl bromide[621d] has been used to prepare a

TABLE 18. Preparation of α,β-unsaturated acids via reaction of olefins with oxalyl bromide

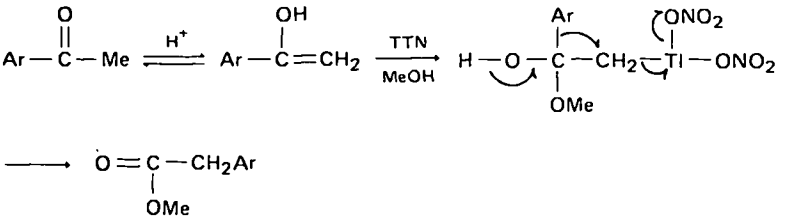
Starting material	Conditions	Carboxylic acid	Yield (%)
Isobutylene	CCl_4, 60°C, 15 h	β,β-Dimethylacrylic	12
Styrene	100°C, 4–5 h	Cinnamic	41
1,1-Diphenylethylene	Dioxane, 110°C, 6.5 h	β-Phenylcinnamic	52
Cyclohexene	110°C, 28 h	Cyclohexenecarboxylic	32
1-Methylcyclopentene	80–100°C, 3–4 h	1-Methylcyclopentenecarboxylic	29
Indene	90°C, 4–5 h	Indenecarboxylic	74
α-Pinene	Dioxane, 60°C, 6.5 h	α-Pinenecarboxylic	42
β-Pinene	Dioxane, 60°C, 6.5 h	β-Pinenecarboxylic	45
d,l-Camphene	CCl_4, 80°C, 5–6 h	Camphene-ω-carboxylic	57
α-Methylcamphene	Dioxane, 100°C, 5–6 h	α-Methylcamphene-ω-carboxylic	45
Anthracene	110–120°C, 8 h	Anthracene-9-carboxylic	52
Acenaphthene	CCl_4, 120–130°C, 18 h	Acenaphthene-5-carboxylic	50
Pyrene	80–90°C, 12 h	Pyrene-3-carboxylic	82
Anisol	100–105°C, 12 h	Anisic	55
α-Naphthol methyl ether	Dioxane, 60°C, 6.5 h	1-Methoxynaphthalene-4-carboxylic	83
β-Naphthol methyl ether	Dioxane, 90°C, 4.5 h	2-Methoxynaphthalene-1-carboxylic	42
	CCl_4, room temp., 4 days		46
	CCl_4, 70°C, 4 h		50



SCHEME 4.

wide variety of α,β-unsaturated acids in good yields. Although this reaction can be envisaged as leading to either α,β-unsaturated acids or α-keto-β,γ-unsaturated acids, the vast majority of olefins tried have produced only α,β-unsaturated acids. The mechanism for this reaction is shown in Scheme 4 and a tabular presentation of the results is given in Table 18.

The most utilitarian reagent to be recently used in the production of carboxylic acids and esters from enolates and acetylenes is thallium(III) nitrate (TTN)[622]. Unlike the Willgerodt–Kindler reaction[623-625] which transforms readily accessible alkyl aryl ketones into ω-arylakanoic acid derivatives, but suffers from the severe limitations of the high temperatures and pressures needed, the tedious and complicated isolation technique and poor yields of product, the use of TTN converts[626] acetophenones in one step into methyl phenyl acetates and avoids the above limitations. The mechanism[626] of this transformation is shown in equation (220)



(220)

and involves acid-catalysed enolization of the acetophenone, followed by oxythallation to produce an unstable alkylthallium dinitrate. Decomposition of this intermediate then proceeds via migration of the aryl substituent, resulting in direct formation of the methyl arylacetate and simultaneous reduction of thallium(III) to thallium(I). The substituted acetophenones used in this reaction are listed in Table 19 along with the yields of the corresponding methyl phenylacetates obtained.

Extension of this approach to the oxidation of acetylenes with TTN has also been reported[627,628]. Studies of this reaction with a variety of acetylenes indicates that the nature of the products obtained depends upon the solvent employed and the structure of the acetylene. Diarylacetylenes are converted into benzils in high yields upon treatment with TTN in either aqueous acidic glyme or in methanol, while dialkylacetylenes afford acyloins in aqueous media and -methoxy ketones in methanol. Monoalkylacetylenes on the other hand, undergo degradation

TABLE 19. Oxidation of acetophenones using thallium(III) nitrate

Starting product	Product	Yield (%)
C_6H_5COMe	$C_6H_5CH_2COOMe$	84
p-FC_6H_4COMe	p-$FC_6H_4CH_2COOMe$	44
p-MeC_6H_4COMe	p-$MeC_6H_4CH_2COOMe$	86
o-$MeOC_6H_4COMe$	o-$MeOC_6H_4CH_2COOMe$	62
3,4-$(MeO)_2C_6H_3COMe$	3,4-$(MeO)_2C_6H_3CH_2COOMe$	88
3-NO_2-4-$MeOC_6H_3COMe$	3-NO_2-4-$MeOC_6H_3CH_2COOMe$	61
p-HOC_6H_4COMe	p-$HOC_6H_4CH_2COOH$[a]	64
p-$C_6H_5CONHC_6H_4COMe$	p-$C_6H_5CONHC_6H_4CH_2COOMe$	66
2-$C_{10}H_7COMe$	2-$C_{10}H_7CH_2COOMe$	94

[a] Obtained by hydrolysis of the crude ester product.

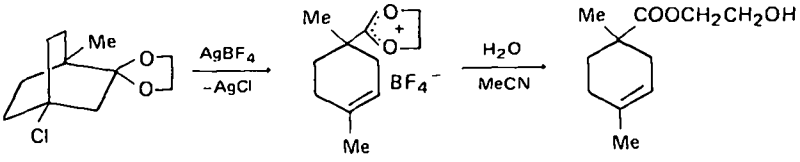
to carboxylic acids containing one carbon atom less than the starting material, while alkylarylacetylenes undergo a smooth oxidative rearrangement in methanol solution to give methyl α-alkylarylacetates. The acetylenes employed[627,628] which gave rise to acids or esters are shown in Table 20 along with the products and yields obtained.

TABLE 20. Oxidation of acetylenes using thallium(III) nitrate

Acetylenes	Products	Isolated Yield, %
$C_6H_{13}C{\equiv}CH$	$C_6H_{13}COOH$	80
$PhC{\equiv}CH$	$PhCH_2COOMe$	17
p-$O_2NC_6H_4C{\equiv}CH$	p-$O_2NC_6H_4CH_2COOMe$	0
p-$MeOC_6H_4C{\equiv}CH$	p-$MeOC_6H_4CH_2COOMe$	61
$PhC{\equiv}CMe$	$PhCHMeCOOMe$	80
$PhC{\equiv}CEt$	$PhCHEtCOOMe$	82
$PhC{\equiv}C(C_3H_7$-$n)$	$PhCH(Pr$-$n)COOMe$	83
$PhC{\equiv}C(C_4H_9$-$n)$	$PhCH(Bu$-$n)COOMe$	77
$PhC{\equiv}CCH_2CH_2Cl$	$PhCH(CH_2CH_2Cl)COOMe$	75
$PhC{\equiv}CCH_2Ph$	$PhCH(CH_2Ph)COOMe$	83
$PhC{\equiv}CCH_2CH_2Ph$	$PhCH(CH_2CH_2Ph)COOMe$	65
$PhC{\equiv}CBr$	$PhCHBrCOOMe$	70

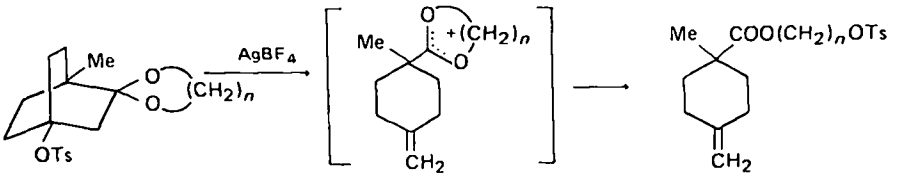
5. *Oxidation of ethers, acetals and ketals*

a. With boron fluorides. Reaction of the ethylene ketal of 1-methyl-4-chlorobicyclo[2.2.2]octan-2-one with silver tetrafluoroborate in absolute ether for 24 hours at room temperature affords[629] the corresponding dioxolonium tetrafluoroborate by silver-catalysed alkyl fragmentation of the ketal (equation 221). Hydro-



(221)

lysis of this salt in aqueous acetonitrile affords a glycol ester. Reaction of the corresponding tosylates leads to isomeric products (equation 222)[629]; however the intermediate salts cannot be isolated.



(222)

A mixture of boron trifluoride etherate and acetic anhydride at 0°C or below has been reported[630,631] to cleave a variety of steroidal methyl ethers. Allylic and homoallylic ethers were found to give their corresponding acetates in excellent yields, while completely saturated ethers gave the corresponding acetate with retention of configuration as the main substitution product, with the epimeric acetate and elimination products also being formed. Thus, using this procedure, cholesteryl methyl ether was converted to cholesteryl acetate in 93% yield, 4-cholesten-7β-ol methyl ether was converted to its acetate which was then hydrolysed to 4-cholesten-7β-ol, 4-cholesten-3β-ol methyl ether afforded 4-cholesten-3β-ol acetate and 3,5-cholestadiene, cholestanyl methyl ether was converted to cholestanyl acetate, cholestan-3α-ol methyl ether afforded cholestan-3α-ol acetate and lupanol methyl ether afforded only a 63% yield of A-nor-$\Delta^{3(5)}$-lupene.

b. With acids. Another interesting preparation of esters may be achieved[632] by the reaction of alkyl *t*-butyl ethers with carboxylic acids. This reaction, which proceeds in the presence of catalytic amounts of various proton-donating agents, e.g. sulphuric or *p*-toluenesulphonic acid, occurs according to equation (223), and has been found to give excellent yields in the cases shown in Table 21. A similar

$$R^1OBu\text{-}t + R^2COOH \xrightarrow{H^+} R^2COOR^1 + CH_2{=}CMe_2 + H_2O \qquad (223)$$

exchange[633] of allylic groups of ethers and esters with active hydrogen compounds has been found to be catalysed by any of the following mixtures: bis(triphenylphosphine)palladium chloride plus sodium phenoxide, palladium acetate plus triphenylphosphine, or zerovalent palladium complexes such as tetrakis(triphenylphosphine)palladium and (maleic anhydride)bis(triphenylphosphine)-

TABLE 21. Preparation of esters via reaction of alkyl *t*-butyl ethers with carboxylic acids

R^1	R^2	R^2COOR^1	Yield (%)
n-Bu	Me	MeCOOBu-*n*	94
$PhCH_2$	Me	$MeCOOCH_2Ph$	94
s-Bu	Me	MeCOOBu-*s*	80
i-Pr	Me	MeCOOPr-*i*	82
$PhCH_2$	*n*-Pr	*n*-$PrCOOCH_2Ph$	87
$PhCH_2$	Ph	$PhCOOCH_2Ph$	53
n-Bu[a]	MeCO	MeCOCOOBu-*n*	86
n-Bu[a]	CF_3	CF_3COOBu-*n*	85

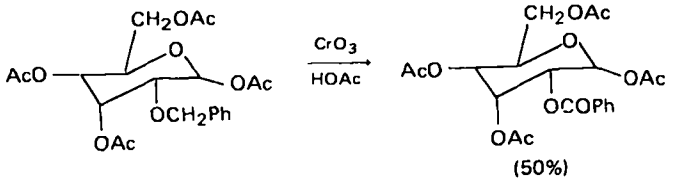
[a] These reactions did not require the addition of any mineral-acid catalyst.

palladium. Typical conversions using this approach include the reaction of methyl acetoacetate with octa-2,7-dienyl phenyl ether in the presence of bis(triphenylphosphine)palladium chloride and sodium phenoxide for two hours at 85°C to yield methyl 2-acetyldeca-4,9-dienoate and methyl 2-(octa-2,7-dienyl)-2-acetyldeca-4,9-dienoate in 84 and 7% yields, respectively, and the reaction of octa-2,7-dienyl phenyl ether with acetic acid, giving the products shown in equation (224).

$$PhOCH_2CH{=}CHCH_2CH_2CH_2CH{=}CH_2 \underset{PhOH}{\overset{AcOH}{\rightleftharpoons}} \quad (224)$$

$$MeCOOCH_2CH{=}CHCH_2CH_2CH_2CH{=}CH_2\ (85\%) + MeCOOCH(CH{=}CH_2)CH_2CH_2CH_2CH{=}CH_2\ (15\%)$$

c. With oxides of chromium. Chromium trioxide in acetic acid has been used to oxidize benzyl ethers of carbohydrates into their corresponding esters in good yields (equation 225)[634], while this same system in methylene chloride has been reported[635] to oxidize alkyl pentadecyl and alkyl hexadecyl ethers to their corresponding acids or esters (equation 226).



(225)

$$Me(CH_2)_nCH_2OCH_2R \xrightarrow[CH_2Cl]{CrO_3,\ HOAc} Me(CH_2)_nCOOR \quad (226)$$

d. With ozone, peracids and peroxides. A comprehensive study[636] of the mechanism of ozonolysis of ethers has been reported[637] where isotope-effect rate studies, competitive relative rate studies on various classes of ethers and product analysis of ozonations using ozone–oxygen and ozone–nitrogen streams have been investigated. Although the product ratios were found to vary depending upon the reaction conditions used, the major products from the reaction of ethers with ozone are esters, aldehydes and/or alcohols as shown in equations (227)–(229).

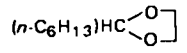
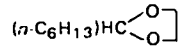
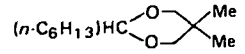
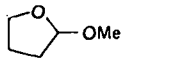
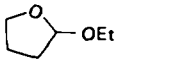
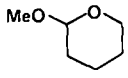
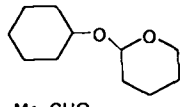
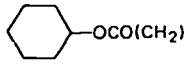
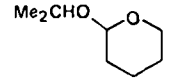
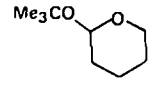
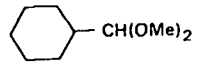
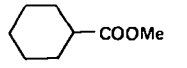
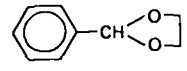
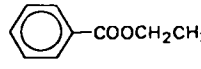
$$MeCH_2OBu\text{-}t \xrightarrow{O_3} HCOOBu\text{-}t + MeCOOBu\text{-}t + t\text{-}BuOH \quad (227)$$

$$PhCH_2OBu\text{-}t \xrightarrow{O_3} PhCOOBu\text{-}t + PhCHO + t\text{-}BuOH \quad (228)$$

$$Me_2CHOCHMe_2 \xrightarrow{O_3} MeCOMe + MeCH(OH)Me + MeCOOCHMe_2 \quad (229)$$

Esters have also been obtained[638,639] upon ozonolysis of acetals, thus ozonolysis of acyclic aldehyde acetals for two hours at room temperature in dichloromethane or ethyl acetate affords their corresponding esters in excellent yields. Cyclic acetals are converted to their corresponding esters within two hours using ozone at −78°C also in dichloromethane or ethyl acetate as solvents, while the conversion of carbohydrates to esters is best accomplished under acylation conditions, e.g. in acetic anhydride–sodium acetate for 15 hours at room temperature. Table 22 lists the various acetals which have been converted to esters using ozone[638,639]. The generality of the above reaction was demonstrated using acetals

TABLE 22. Acetals converted to esters by ozone

Acetal	Product	Yield (%)
$(n\text{-}C_6H_{13})CH(OMe)_2$ $(n\text{-}C_6H_{13})CH(OEt)_2$	$(n\text{-}C_6H_{13})COOMe$ $(n\text{-}C_6H_{13})COOEt$	90 94
	$(n\text{-}C_6H_{13})COOCH_2CH_2OH$	100
	$(n\text{-}C_6H_{13})COOCH_2CH_2CH_2OH$	97
	$(n\text{-}C_6H_{13})COOCH_2CMe_2CH_2OH$	98
	$MeCOOCH_2(CH_2)_2COOMe$	85
	$MeCOOCH_2(CH_2)_2COOEt$	87
Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside	Methyl 2,3,4,5,6-penta-*O*-acetyl-D-gluconate	95
Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside	Methyl 2,3,4,5,6-penta-*O*-acetyl-D-mannonate	74
Methyl 2,3,4,6-tetra-*O*-acetyl-β-*O*-galactopyranoside	Methyl 2,3,4,5,6-penta-*O*-acetyl-D-galactonate	92
2-Deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside	2-Deoxy-3,4,6-tri-*O*-acetyl-5-hydroxy-D-gluconate	–
	$MeOOC(CH_2)_3CH_2OH$	97–99
		91
	$Me_2CHOOC(CH_2)_3CH_2OH$	95
	$Me_3COOC(CH_2)_3CH_2OH$	91
		98
		100
Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside	Methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-gluconate	81
Methyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-xylonate	78
Methyl 2,3,4-tri-*O*-acetyl-α-D-arabinopyranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-arabonate	95
Methyl 2,3,4-tri-*O*-acetyl-β-D-arabinopyranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-arabonate	71
Methyl 3,4,5-tri-*O*-acetyl-β-D-ribofuranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-ribonate	90

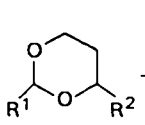
made from various aldehydes, such as *n*-heptanal, cyclohexanecarboxaldehyde and benzaldehyde, and different types of alcohols, such as methanol, ethanol, ethylene glycol, 1,3-propanediol and 2,2-dimethyl-1,3-propanediol.

Treatment of acetals with peracetic acid alone or catalysed by sulphuric acid has been found[640] to afford the corresponding ester. Reaction of crotonaldehyde di-*n*-butyl acetal with peracetic acid afforded[640] a 73% yield of *n*-butyl crotonate (equation 230), while sulphuric acid-catalysed peracetic acid oxidation of *n*-butyr-

$$MeCH{=}CHCH(OC_4H_9\text{-}n)_2 \xrightarrow[EtOAc]{MeCO_3H} MeCH{=}CHCOO(C_4H_9\text{-}n) \qquad (230)$$

aldehyde diethyl acetal gave a 69% yield of ethyl butyrate. Similar acid-catalysed oxidation of benzaldehyde diethyl acetal, β-phenyl-β-ethoxypropionaldehyde and 2-(β-styryl)-4-methyl-1,3-dioxolane afforded[640] ethyl benzoate (90%), ethyl β-phenyl-β-ethoxypropionate (61%) and propylene glycol monocinnamate (28%), respectively. Oxidation of acetals using air or oxygen to yield acids has also been reported[641].

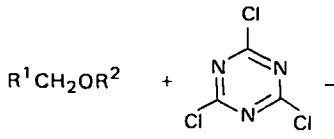
Di-*t*-butyl peroxide has also been found[642] to be effective in the oxidative isomerization of 2- and 4-substituted 1,3-dioxanes into esters and aldehydes when the reaction was performed at 90–150°C (equation 231).



$$\xrightarrow{(Me_3CO)_2} R^1COOCH_2CH_2CH_2R^1 + R^1COOCHR^2Et + EtCOR^2 + R^1CHO \qquad (231)$$

Ethers of the general formula $R^1CH_2OR^1$ have also been reported[643] to give alcohols, acids and carboxylates when treated with molecular oxygen.

e. With trichloroisocyanuric acid. A direct oxidation of aliphatic ethers of the general formula $R^1CH_2OR^1$ to carboxylic acid esters has been reported[644,645] to occur in good yield using trichloro-1,3,5-triazine (trichloroisocyanuric acid) in water at 3°C for 3–20 hours (equation 232). Using this procedure, symmetrical ethers are converted to a single ester product, whereas unsymmetrical ethers are converted to esters which are selectively determined by steric effects, namely Newman's 'rule of six'. The esters prepared by this method are shown in Table 23.

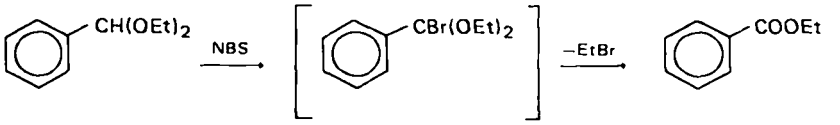


$$R^1CH_2OR^2 + \longrightarrow R^1COOR^2 \qquad (232)$$

TABLE 23. Preparation of esters from ethers using trichloro-1,3,5-triazine

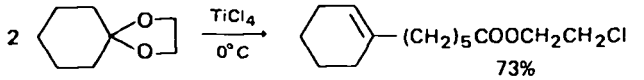
Ether	Product	Yield (%)
EtOEt	MeCOOEt	49
n-BuOBu-*n*	*n*-PrCOOBu-*n*	50–100
$PhCH_2OEt$	PhCOOEt	5
Me_2CHCH_2OEt	$Me_2CHCOOEt$	83
Me_2CHOEt	$MeCOOCHMe_2$	55

f. With inorganic and organic halides. An interesting reaction, which appears to be general for acetals, was observed[646] when benzaldehyde diethyl acetal was allowed to react with an equimolar quantity of *N*-bromosuccinimide (NBS) at 40°C. The product isolated from this reaction was ethyl benzoate suggested to be formed via the mechanism shown in equation (233).

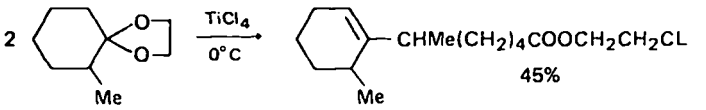


(233)

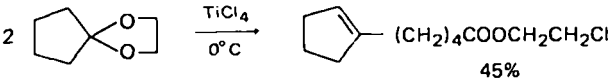
Reaction of the ethylene acetals of cyclic ketones in dichloromethane at 0°C with titanium(IV) chloride has been reported[647] to afford the 2-chloroethyl esters of a carboxylic acid containing double the number of carbon atoms of the original ketone (equation 234). It was also reported[647] that under the same conditions open-chain ketones afforded 2-chloroethyl carboxylates in which the alkoxycarbonyl group is attached to one of the 2-substituents of the original 1,3-dioxolane (equation 235). A mechanism for this series of reactions is proposed. Similar



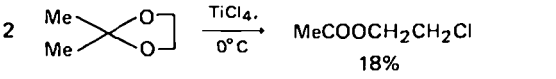
(234a)



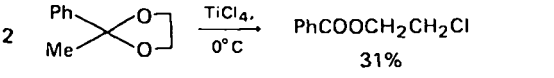
(234b)



(234c)

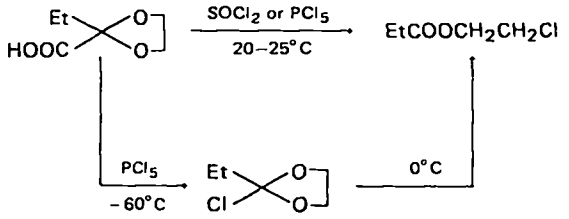


(235a)

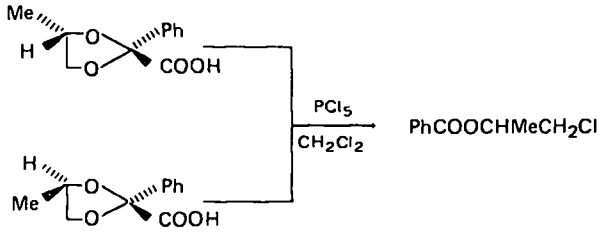


(235b)

compounds have been prepared[648] via a rather unique stereospecific reaction using thionyl chloride or phosphorus pentachloride. Thus, treatment of 2-carboxy-2-ethyl-1,3-dioxolane with either chloride at room temperature affords 2-chloroethyl propionate directly, while reaction with phosphorous pentachloride in methylene chloride at −60°C first yields 2-chloro-2-ethyl-1,3-dioxolane which rapidly rearranges to 2-chloroethyl propionate upon warming to 0°C (equation 236). The high regiospecificity and stereospecificity of this reaction can best be seen from the reaction of a 3:2 *trans*:*cis* mixture of 2-carboxy-4-methyl-2-phenyl-1,3-dioxolane with phosphorus pentachloride in methylene chloride which affords an 85–92% yield of 1-chloro-2-propyl benzoate with no trace of isomers present in the product (equation 237). Similarly, D(−)-2-carboxy-2,4,5-trimethyl-1,3-dioxolane and 2-carboxy-2,5,5-trimethyl-1,3-dioxane upon treatment with phosphorus penta-

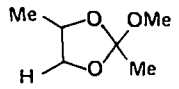
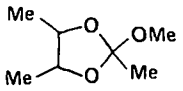
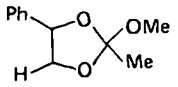
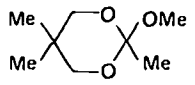
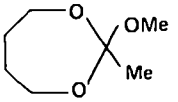


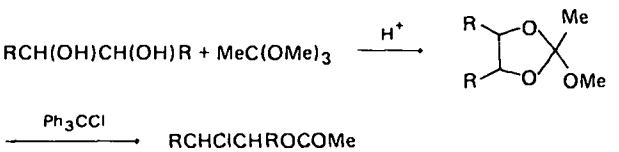
(236)



(237)

TABLE 24. Reaction of cyclic *ortho* esters with trityl chloride

ortho Ester	Product	Yield (%)
	$MeCH(OCOMe)CH_2Cl$	89
	$MeCHClCH(OCOMe)Me$	90
	$PhCHClCH_2OCOMe$	93
	$ClCH_2CMe_2CH_2OCOMe$	83
	$Cl(CH_2)_4OCOMe$	38



(238)

chloride afford L(+)-*erythro*-3-chloro-2-butyl acetate and 3-chloro-2,2-dimethylpropyl acetate, respectively.

Reaction of cyclic *ortho* esters with trityl chloride in methylene chloride at reflux has also been reported[649] to afford the acetates of the chlorohydrins in high yields (equation 238) (Table 24). These reactions were also found to be regiospecific and stereospecific, yielding the same stereochemical results as reported above in the ketal acid reaction.

g. With miscellaneous reagents. Several of the reactions discussed in this section which afford acids or esters from ethers or acetals are not oxidation reactions *per se*, but appear overall to be oxidative conversions and are thus included in this section.

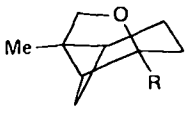
Reaction of 1-alkoxy-1,2-diacetoxyalkanes with potassium cyanide and ammonium chloride in aqueous ammonia, followed by subsequent hydrolysis of the resultant unisolated nitrile using concentrated hydrochloric acid affords α-amino-β-hydroxy carboxylic acids[650]. If primary amines are substituted for ammonia in this reaction, the corresponding α-alkylamino-β-hydroxy carboxylic acids are obtained. This overall procedure is a modification of the Strecker synthesis of amino acids and is widely applicable affording good yields for the preparation of serine and its higher homologues (Table 25).

TABLE 25. Preparation of amino acids via modified Strecker synthesis

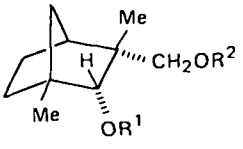
$$R^1CH(OAc)CH(OAc)OEt + H_2NR^2 + KCN \longrightarrow R^1CH(OH)CH(NHR^2)CN \xrightarrow[H_2O]{HCl} R^1CH(OH)CH(NHR^2)COOH$$

R^1	R^2	Yield (%)
H	H	51
Me	H	83
Et	H	74
n-Pr	H	67
n-$C_{10}H_{21}$	H	46
H	Me	27
H	Et	32
H	*n*-Bu	47

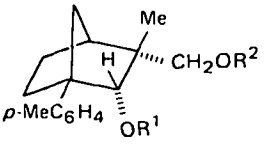
Treatment of a series of tricyclic 2,8-nopinyl ethers with a variety of reagents has lead to formation of acetate esters. Thus, treatment of 6,9-dimethyl-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (26, R = Me) with acetyl toluene-*p*-sulphonate in acetonitrile for 14 hours at room temperature affords[651] 80% of 1,3-dimethyl-2α-*p*-tolylsulphonyloxynorbornan-3α-ylmethyl acetate (27; $R^1 = SOC_6H_4Me$-*p*, R^2 = Ac). If the same starting material (26, R = Me) was allowed to react with boron trifluoride–etherate in acetic anhydride a 90% conversion to 2α-acetoxy-1,3-dimethylnorbornan-3α-ylmethyl acetate (27, $R^1 = R^2$ = Ac) was obtained[651].



(26)

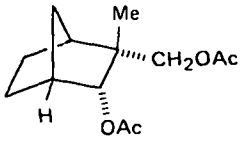


(27)



(28)

Reaction of 9-methyl-6-*p*-tolyl-7-oxatricyclo[4,3,0,$0^{3,9}$]nonane (**26**, R = C_6H_4Me-*p*) with the same reagents at 0°C for one hour afforded 3α-hydroxymethyl-3-methyl-1-*p*-tolylnorbornan-2α-yl acetate (**28**, R^1 = Ac, R^2 = H), while if the reaction was performed at −20°C followed by acetylation, using acetic anhydride in pyridine, 3α-acetoxymethyl-3-methyl-1-*p*-tolylnorbornan-2α-yl acetate (**28**, R^1 = R^2 = Ac) was obtained in 95% yield. The most interesting result obtained in this study[651] was the consequence of rearrangement of 9-methyl-7-oxatricyclo[4,3,0,$0^{3,9}$]nonane (**26**, R = H) to *endo*-3α-acetoxymethyl-3-methylnorbornan-2α-yl acetate (**29**) and *exo*-7-acetoxymethyl-7-methylnorbornan-2β-yl acetate (**30**) upon reaction with boron trifluoride–etherate in acetic anhydride for one hour at 0°C.



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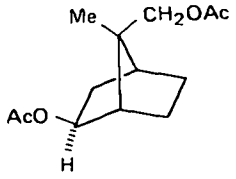
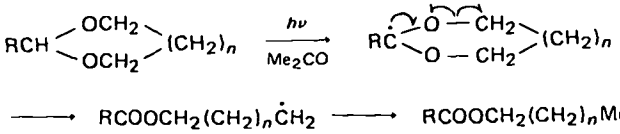


(30)

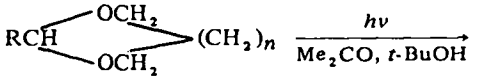
Photochemical conversions of acetals to the corresponding carboxylic esters have also been reported[652] and are shown in Table 26. These conversions may be regarded as isomerizations by an intramolecular oxidation–reduction, for which a mechanism (equation 239) was suggested where the acetone plays a vital role in the



(239)

initiation step, consisting of a hydrogen abstraction from the carbon attached to the oxygen atom. In the absence of acetone, rather poor yields of the esters are obtained.

TABLE 26. Preparation of esters via photochemical treatment of acetals



Acetal			
R	*n*	Product	Yield (%)
$Me(CH_2)_4$–	0	Ethyl hexanoate	36
$Me(CH_2)_6$–	0	Ethyl octanoate	55
$Me(CH_2)_8$–	0	Ethyl decanoate	33
$PhCH_2$–	0	Ethyl phenylacetate	35
$Ph(CH_2)_2$–	0	Ethyl hydrocinnamate	30–50
$Me(CH_2)_6$–	1	Propyl octanoate	23
$Ph(CH_2)_2$–	1	Propyl hydrocinnamate	14

6. Oxidation of ketones

a. With peracids (Baeyer–Villiger reaction). The Baeyer–Villiger reaction, which involves the oxidation of carbonyl compounds with a peracid, has been reviewed[652-657]. Although this reaction is applicable to both aldehydes and ketones it has been used largely with ketones and because of this fact it will be presented in this section. A variety of reagents have been used to effect ester formation from ketones, and this discussion will centre on the reagent chosen for the conversion reported.

Treatment of cyclanones in ethanol with Caro's acid affords[658] the ethyl esters of ω-hydroxy aliphatic acids with the same carbon content as the starting material albeit in fair yields. Solutions of $K_2S_2O_8$ in 50% sulphuric acid (effectively H_2SO_5) has been reported[659] to give quantitative yields of the Baeyer–Villiger products for a variety of simple aliphatic ketones. The migration aptitudes of hydrogen and simple alkyl groups in the Baeyer–Villiger oxidation of ketones has been studied[659-661] and has been found to be in the order propyl ≈ H > ethyl ≫ methyl. Peroxymonosulphuric acid (Caro's acid) has also been used to effect the Baeyer–Villiger reaction with a variety of aldehydes[423,424,434,441].

Peroxyformic acid has been found[662] an effective oxidizing agent in converting hydroxybenzaldehydes into hydroxyphenyl formates, while peracetic acid has been found to be an effective oxidizing agent under a variety of conditions. In the presence of acetic anhydride, peracetic acid treatment of salicylaldehyde affords[662] an 88% yield of *o*-hydroxyphenyl formate. Addition of a few drops of sulphuric acid to peracetic acid allows a 90% conversion[663] of benzaldehyde diethyl acetal to ethyl benzoate, while in a mixture of glacial acetic and sulphuric acids, peracetic acid oxidizes *p*-nitrobenzophenone to phenyl *p*-nitrobenzoate in 95% yield[664]. Treatment of crotonaldehyde dibutylacetal at 60°C with peracetic acid in ethyl acetate yields a 73% conversion to butyl crotonate[665]. Oxidation of cycloheptanone and cyclooctanone with peracetic acid in an inert solvent like ethyl acetate affords a good yield of the corresponding dibasic acids[666], but using the same oxidizing mixture with cyclopentanone and various cyclohexanones affords high yields of monomeric lactones. In contrast, higher ketones such as cyclododecanone are converted[667] into mixtures of lactones and dibasic acids using excess peracetic acid in acetone and sulphuric acid.

Perbenzoic acid in moist chloroform has been used to convert simple methyl ketones into their corresponding acetate esters (equation 240)[668]. Although the

$$\mathrm{MeCOR} \xrightarrow[\mathrm{CHCl_3}]{\mathrm{PhCO_3H}} \mathrm{MeCOOR} \qquad (240)$$

ketones reported above all gave good yields of ester, similar treatment of cyclopropyl methyl ketone and acetomesitylene did not afford the corresponding acetates. Treatment of propiophenone with perbenzoic acid in moist chloroform[668] affords a 73% yield of phenyl propionate, an indication that simple ketones other than methyl ketones are also susceptible to reaction. Perbenzoic acid has been used most extensively in the oxidation of steroids. The acetate of allopregnanol-3-one-20 has been converted[669] into its corresponding diacetate using perbenzoic acid, while the oxidation of 17-acetyl steroids to the corresponding 17-acetates has also been reported[670] using perbenzoic acid. Pregnane-3α-ol-11,20-dione acetate has been reported[670] to be oxidized in 85% yield to etiocholane-3α,17α-diol-11-one diacetate.

TABLE 27. Conversion of ketones to esters using trifluoroperoxyacetic acid

Ketone	Ester	Yield (%)
Methyl ethyl	Ethyl acetate	72
Diethyl	Ethyl propionate	78
Methyl *n*-propyl	*n*-Propyl acetate	78
Methyl isopropyl	Isopropyl acetate	81
Methyl *n*-butyl	*n*-Butyl acetate	81
Methyl isobutyl	Isobutyl acetate	84
Methyl *n*-amyl	*n*-Amyl acetate	87
Methyl cyclopropyl	Cyclopropyl acetate	53
Di-*n*-propyl	*n*-Propyl butyrate	80
Diisobutyl	Isobutyl isovalerate	81
Benzophenone	Phenyl benzoate	88

Although it was originally reported[652] that simple ketones of the type $R^1CH_2COCH_2R^2$ could not be oxidized to their corresponding esters with conventional reagents such as peracetic, perbenzoic or Caro's acids, trifluoroperoxyacetic acid has been shown[671] to be an effective reagent for this conversion. Oxidation of the ketones listed in Table 27 was accomplished in good yields by the addition of the ketone to a solution of peroxytrifluoroacetic acid prepared from trifluoroacetic anhydride and 90% hydrogen peroxide in methylene chloride containing disodium hydrogen phosphate. This reagent has also been used[550] in the Baeyer–Villiger oxidation of (1-methyl-*O*-carborane-3-yl)phenyl ketone which resulted in the migration of the 1-methyl-3-*O*-carboranyl group.

A similar reagent, hexafluoroacetone–hydrogen peroxide, has also been reported[672] to be effective in the oxidation of a variety of ketones to esters (Table 28).

Using a solution of 90% hydrogen peroxide in boron trifluoride etherate, a rapid conversion of simple aliphatic ketones to esters has been achieved in good yields at room temperature (Table 29)[673]. Although small amounts of the alcohols formed by hydrolysis of the esters were also obtained, the yield of esters is still acceptable. The nuclear oxidation of *m*-xylene and toluene was also effected with this reagent.

A novel reagent which has found use in the Baeyer–Villiger oxidation of ketones is permaleic acid formed[674] by reaction of maleic anhydride with hydrogen peroxide in an inert solvent. Although permaleic acid is not quite as potent a peracid as trifluoroperacetic acid and does not afford as high a yield of esters as

TABLE 28. Conversion of ketones to esters using hexafluoroacetone and hydrogen peroxide

Ketone, etc.	Ester, etc.	Yield (%)
Methyl isobutyl	Isobutyl acetate	73
Methyl *n*-amyl	*n*-Amyl acetate	81
Cyclohexanone	Caprolactone	50
Acetophenone	Phenyl acetate	34
Aniline	Nitrobenzene	65
Pentafluoroaniline	Decafluorozaobenzene	10
Mesitylene	Mesitol	40

TABLE 29. Preparation of esters using boron trifluoride and hydrogen peroxide

Ketone, etc.	Ester, etc.	Yield (%)
2-Octanone	*n*-Hexyl acetate	62
Methyl isobutyl	Isobutyl acetate	58
Diethyl	Ethyl propionate	60
2-Heptanone	*n*-Amyl acetate	60
m-Xylene	2,6-Dimethyl-3-hydroxybenzoquinone	–
Toluene	Cresol	93

indicated in Table 30, it has the advantage of being easily prepared and having a reduction product which is insoluble in the oxidation media used.

Commercially available *m*-chloroperbenzoic acid has found extensive use as the reagent of choice in the Baeyer–Villiger oxidation of steroids[422,675-679], and in the introduction of the carboxylate linkage into olefins[680]. This latter reaction involves the reaction of dicyclohexylborane with a number of olefins containing a variety of functional groups, followed by carbonylation of the resulting organoborane in water to yield a functionally substituted cyclohexyl monoalkyl ketone. Treatment of these ketones with *m*-chloroperbenzoic acid affords conversions to the corresponding substituted ester, provided the substituents do not react with any of the reagents used.

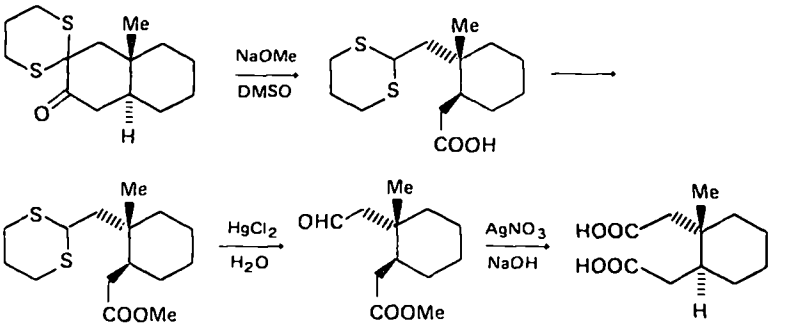
TABLE 30. Preparation of esters from ketones using permaleic acid

Ketone	Ester	Yield (%)
Methyl isobutyl	Isobutyl acetate	72
Diisobutyl	Isobutyl isovalerate	83
2-Octanone	*n*-Hexyl acetate	71
Cyclooctanone	ω-Hydroxyoctanoic acid lactone	67
Oestrone acetate	Estronolactone acetate	40
Benzophenone	Phenyl benzoate	70
Acetophenone	Phenyl acetate	70
Desoxybenzoin	Benzyl benzoate + phenyl phenylacetate (7 : 1)	75

b. With base. Reaction in the liquid phase of an α-nitro ketone with an alcohol and base affords organic esters in good yields[681]. Thus, reaction of 1-nitro-2-tridecanone with sodium methoxide for two hours under reflux produces a 90% yield of methyl dodecanoate, while reaction of 1-nitro-2-butanone with sodium isopropoxide for 16 hours at 60°C affords a comparable yield of isopropyl propionate. Other bases used include aniline, α-picoline and triethylamine, while using tertiary alcohols as solvents affords no reaction.

Using sodium methoxide in dimethyl sulphoxide causes carbon to carbon bond cleavage in the keto dithiane shown in equation (241) to afford the corresponding acid directly[682]. Conversion of the acid product to the corresponding ester followed by treatment with aqueous mercuric chloride produces the aldehyde ester, which upon treatment with basic silver nitrate gives the dibasic acid indicated[682].

When alcohol-free sodium methoxide or isopropoxide is allowed to react with α-bromo-*s*-alkyl ketones in ether as the solvent, a widely general reaction occurs which produces the ester of the tertiary acid (equation 242)[683,684]. The



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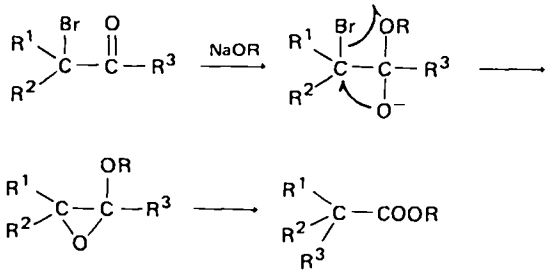

(242)

mechanism proposed for the conversion involves the intermediate formation of an ethylene oxide which then produces the ester. Reported in Table 31 are the ketones which have been found to undergo the conversion.

Reaction of an ether suspension of sodium methoxide at 10–20°C with 3,4-dibromo-3-methyl-2-butanone for 30 hours affords a mixture containing 42% of methyl β,β-dimethylacrylate and 16% methyl β-methoxyisovalerate; however with a reaction time of 2.5 hours, a mixture containing the same products but in a ratio of 64% to 2% was obtained[685]. Similarly, using the shorter reaction time 3,4-dibromo-3-methyl-2-pentanone affords 15% of 3-methyl-3-penten-2-one and 55% of methyl *trans*-3-methyl-3-pentenoate, while 1-acetyl-1,2-dibromocyclohexane affords 19% of methyl-1-cyclohexenyl ketone and 34% of methyl 1-cyclohexenyl-acetate[685].

Although the most common base systems used to convert ketones into acids or esters contain alkoxides in a variety of solvents as discussed above, metal hydroxide in hexamethylphosphoramide or methanol have also been used to effect similar conversions. Using either sodium or potassium hydroxide in hexamethylphosphoramide at 23–80°C a series of C_5–C_{12} aliphatic ketones were autooxidized to their

TABLE 31. Preparation of esters from ketones using sodium alkoxides

Ketone	Base	Product	Yield (%)
3-Bromo-3-methyl-2-butanone	NaOMe	Methyl trimethylacetate	39
3-Bromo-3-methyl-2-butanone	NaOPr-*i*	Isopropyl trimethylacetate	64
3-Bromo-3-methyl-2-butanone	NaOEt	Ethyl trimethylacetate	61.3
4,4-Dimethyl-3-bromo-2-pentanone	NaOMe	Methyl methyl-*t*-butylacetate	73
3-Bromo-3-methyl-4-heptanone	NaOMe	Methyl methylethylpropylacetate	<75

corresponding dibasic acids in moderate to excellent yields, while acetophenone afforded benzoic acid under the same conditions[686]. This study indicated that the choice of solvent for these reactions is critical and that the ease of oxidation with respect to solvent was in the order HMPA > *t*-butyl alcohol >>> water. It was also found that lithium hydroxide was not an effective base for these oxidations.

Reaction of potassium hydroxide in methanol with 16,17-dibromopregnan-3β-ol-20-one acetate has been reported to afford 3β-hydroxy-$\Delta^{17,20}$-pregnen-21-oic acid and its methyl ester by an interesting rearrangement (equation 243)[687].

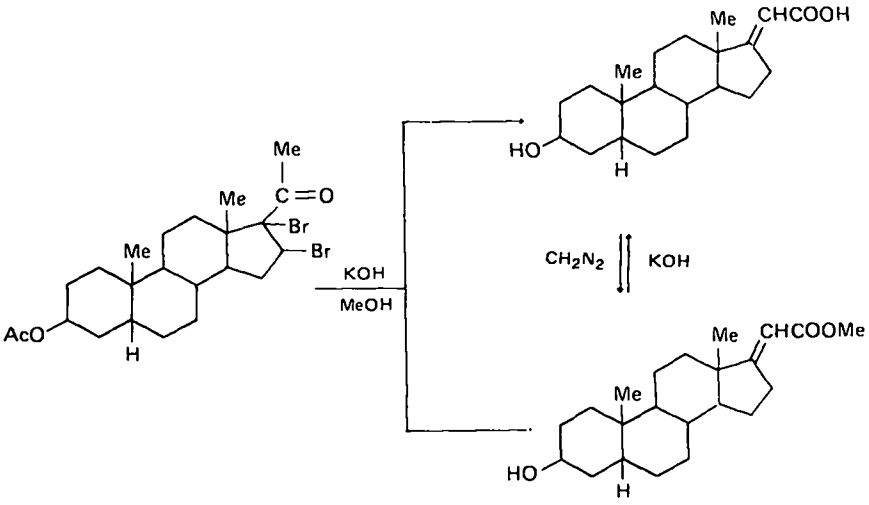

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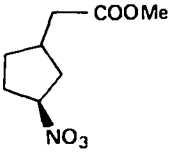
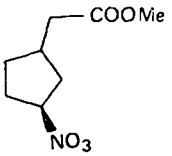
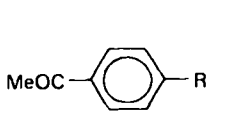
TABLE 32. Preparation of esters from cyclic ketones using ceric ammonium nitrate

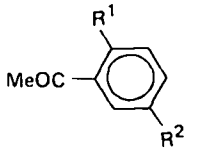
Ketones	Products	Yield (%)
Cyclohexanone	Methyl 5-nitrohexanoate	20
	Methyl 6-nitrohexanoate	30
Cyclopentanone	Methyl 5-nitropentanoate	12
	Methyl 4-nitropentanoate	8
	Methyl 4-nitrobutanoate	17
	Methyl 3-nitrobutanoate	13
Norbornanone		30
		20

c. With ceric ammonium nitrate. A study of the kinetics and mechanism of the ceric ammonium nitrate oxidation, under drastic conditions, of carbonyl compounds such as aldehydes and ketones has been reported[688]. The ultimate products from these reactions are formic acid and carbon dioxide and it appears at first glance that this oxidation is not of synthetic importance. However, treatment of cyclic ketones with four molar equivalents of ceric ammonium nitrate at 60°C in aqueous acetonitrile afforded[689] mixtures of nitrocarboxylic acids in about 50% yields as indicated in Table 32. Since these products could be treated with diazomethane, converted to their corresponding methyl esters and then separated without much difficulty, this method provides a useful approach to their preparation, albeit in low yields.

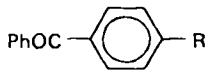
d. With nitric acid. In order to establish the structure of the various ketones prepared from Friedel–Crafts acylation of mono- and di-*s*-alkyl benzenes, oxidation to their corresponding benzene carboxylic acids was accomplished using dilute nitric acid, chromic acid or sodium dichromate–sulphuric acid–acetic acid mixtures[690]. The ketones oxidized are the acetophenones and benzophenone shown below, and with the sodium dichromate–sulphuric acid–acetic acid mixture the



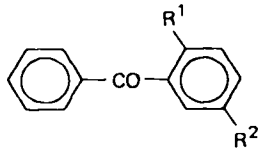
R
s-Butyl
s-Amyl
s-Octyl



R^1	R^2
Me	*s*-Butyl
s-Butyl	*s*-Butyl
s-Amyl	*s*-Amyl



R
s-Butyl
s-Amyl
s-Dodecyl



R^1	R^2
s-Butyl	*s*-Butyl

alkyl and dialkylacetophenones gave terephthalic acid. Oxidation of the dialkylacetophenones with dilute nitric acid afforded the corresponding 4-alkylisophthalic acids, while the *p-s*-alkylacetophenones were oxidized to their corresponding *p-s*-alkylbenzoic acids using nitric acid. Chromic acid oxidation converts the 2,5-di-*s*-butylacetophenone to trimellic acid, and the *p*-alkylbenzophenones and the 2,5-di-*s*-butylbenzophenone to *p*-benzoylbenzoic acid and benzoylterephthalic acid, respectively.

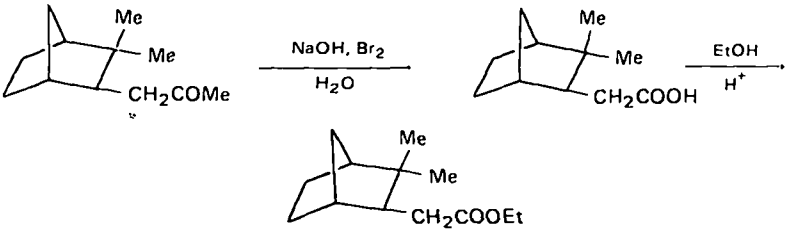
Dilute nitric acid oxidation of 4,4-diethyl-3-hexanone is reported[691] to yield a 71% conversion to 2,2-diethylbutanoic acid.

e. With alkali and halogen (haloform reaction). The haloform reaction[692] involves the conversion of the acetyl group in methyl ketones or acetaldehyde into the carboxyl group by cleavage of the acetal with halogen and a base. Various combinations of chlorine, bromine or iodine and sodium or potassium hydroxide, as their corresponding hypohalites, have been used as reagents in this reaction, and in some cases commercial bleaching agents have been used successfully. During the conversion of methyl β-naphthyl ketone to 2-naphthoic acid, which was accomplished in 87–88% yield[693], using aqueous sodium hydroxide and chlorine, it was established that excess chlorine in the hypohalite reagent is not desirable.

A variety of aliphatic methyl ketones have been used as starting materials in the haloform reaction and have afforded good to excellent yields of their corresponding carboxylic acids. Using aqueous sodium hydroxide and bromine as the oxidizing reagent effects the conversion of pinacolone to trimethylacetic acid (pivalic acid) in 71–74% yield[694], 4,4-dimethyl-3-ethyl-2-pentanol to ethyl-*t*-butylacetic acid in

$$t\text{-BuCHEtCH(OH)Me} \xrightarrow[H_2O]{Br_2,\ NaOH} t\text{-BuCHEtCOOH} \qquad (244)$$

38% yield (equation 244)[695] and 1-(2,2-dimethyl-3-norbornyl)propanone to 3-carboxymethylene-2,2-dimethylnorbornane which was then converted into its ethyl ester in 80% yield (equation 245)[696]. That the presence of unsaturation does not affect the course of the haloform reaction is illustrated by the conversion of mesityl oxide to β,β-dimethylacrylic acid in 49–53% yield using potassium hydroxide and chlorine (equation 246)[697].



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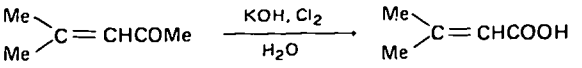
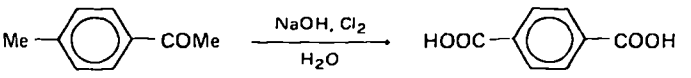


(246)

The only complication which arises when aryl methyl ketones are used in the haloform reaction occurs when methylene or methyl groups are attached to the aromatic nucleus. In these cases the methylene or methyl group as well as the acetyl group are oxidized to carboxyl groups. Thus, *p*-methylacetophenone affords terephthalic acid in 47% yield (equation 247), while 2-acetyl-9,10-dihydrophenanthrene affords 2,2′,4-tricarboxylbiphenyl in 49% yield (equation 248)[698]. Aside



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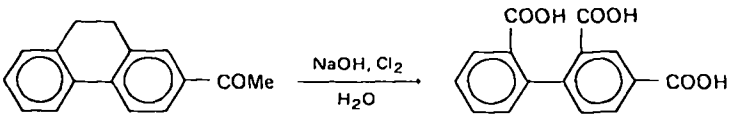
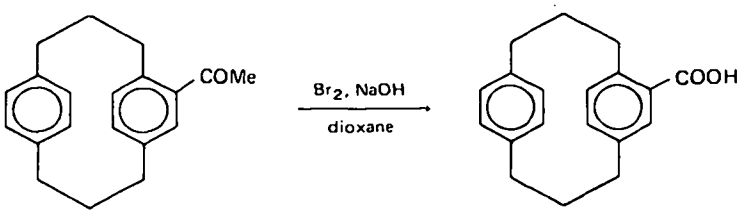


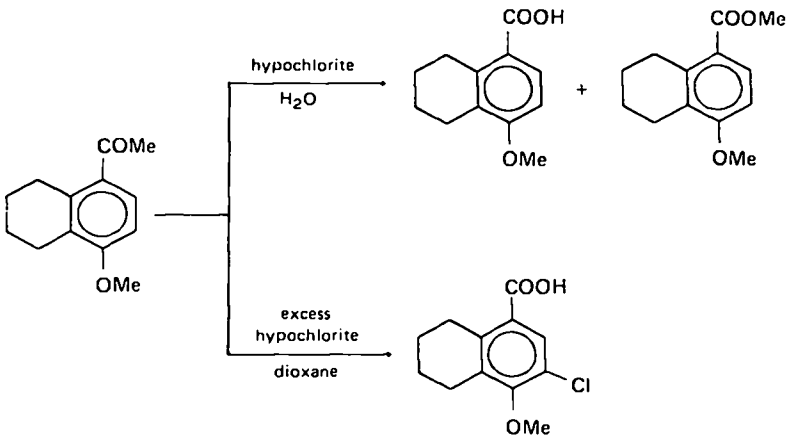
(248)

from this difficulty, the oxidation of other simple or substituted aryl methyl ketones via the haloform reaction occurs in the usual manner. Treatment of acetophenone with chlorine affords dichloroacetophenone which upon treatment with aqueous sodium hydroxide affords a 76–87% yield of mandelic acid[699]. Reaction of *p*-bromoacetophenone with bromine affords *p*,α,α-tribromoacetophenone, which upon treatment with aqueous sodium hydroxide affords[700] *p*-bromomandelic acid in 69–83% yield. Alicyclic groups do not change the course of reaction, since treatment of 5-acetyl[3.3]paracyclophane in dioxane with bromine and aqueous potassium hydroxy affords 5-carboxy[3.3]paracyclophane in 96% yield (equation 249)[701], and treatment of 5-acetyl-8-methoxytetralin with calcium hypochlorite in aqueous potassium hydroxide affords 8-methoxy-5-tetralincarboxylic acid along with its corresponding methyl ester, 5-carbomethoxy-8-meth-



(249)

oxytetralin (equation 250)[702]. If excess hypohalite in dioxane is used in the latter reaction, chlorination of the aromatic nucleus occurs affording 7-chloro-8-methoxy-5-tetralincarboxylic acid.



(250)

Alkyl ketones which are higher than methyl have also been reported to undergo the haloform reaction as long as there are two α-hydrogen atoms present. Thus, propiophenone affords a 64% yield of benzoic acid when treated with bromine and aqueous sodium hydroxide[703,704]. During the investigation of the mechanism of this conversion[704] 1-phenyl-1,2-propanedione was also allowed to react with this mixture of reagents and a 91% conversion to benzoic acid was obtained.

Heterocyclic molecules have also been reported to undergo typical haloform reactions, such as the conversion of *n*-propyl 2-thienyl ketone to 2-thiophenic acid[703], 5-methyl-2-propionylthiophene to 5-methyl-2-thiophenic acid (67%)[703], and 2-acetyl-5-*n*-butylpyridine ketone to 5-*n*-butylpyridine-2-carboxylic acid (90%)[705].

Both aliphatic and alicyclic β-diketones have been treated under haloform reaction conditions and the results obtained are interesting. Since aliphatic β-diketones cleave under the conditions of the haloform reaction, they are converted to carboxylic acids according to equation (251). On the other hand, cyclic

$$R^1OC-CH_2COR^2 \xrightarrow[H_2O]{X_2,\ NaOH} R^1COOH + R^2COOH \qquad (251)$$

β-diketones afford diacids upon treatment with alkali and halogen, for example treatment of methone (5,5-dimethyl-1,3-cyclohexanedione) with aqueous sodium hydroxide and chlorine gives an 81–91% yield of β,β-dimethylglutaric acid[706].

Other more interesting examples of the haloform reaction include the conversion of 1,1′-diacetylferrocene to ferrocene-1,1′-dicarboxylic acid in 85–90% yield using

sodium hypobromite in aqueous dioxane at 0–5°C[707], the conversion of the methyl ketone formed by ozonolysis of hardwickiic acid to its corresponding carboxylic acid using sodium hypobromite[578], and the conversion of 3β-acetoxy-5-pregnen-20-one (pregnenolone acetate) to 3β-acetoxyetienic acid (3β-acetoxy-5-androstene-17β-carboxylic acid) in 55–63% yield also using sodium hypobromite[708].

Limited bromination of methyl ketones, followed by reaction with potassium bicarbonate affords *cis*-α,β-unsaturated acids (equation 252)[709].

$$RCH_2COMe \xrightarrow{Br_2} RCHBrCOCH_2Br \xrightarrow[2.\ HCl]{1.\ KHCO_3} \begin{matrix} R & & COOH \\ & C=C & \\ H & & H \end{matrix} \qquad (252)$$

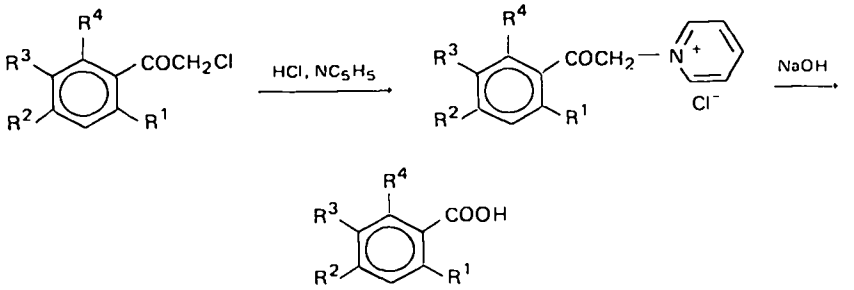
f. With iodine–pyridine and alkali. An alternative method to the haloform reaction for the conversion of acetyl groups into carboxyl groups has been reported[710], which involves the reaction with iodine in the presence of the base, pyridine. This reaction (equation 253), which gives good yields of carboxylic acid

$$ArCOMe \xrightarrow[C_5H_5N]{I_2} (ArCOCH_2\overset{+}{N}C_5H_5)I^- \xrightarrow[2.\ H^+]{1.\ NaOH} ArCOOH \qquad (253)$$

products, has been found effective in cases where the haloform reaction cannot be used, such as in the preparation of a variety of aromatic[710] and hydroxybenzoic acids[711]. Its mechanism parallels that of the haloform reaction[710,711] and involves substitution of iodine for an α-hydrogen to produce the α-pyridinium iodide salt ($ArCOCH_2\overset{+}{N}C_5H_5I$) which is attacked by the hydroxide ion to give an anion which then cleaves to produce the carboxylic acid.

Some examples of the use of this reaction include the preparation of: 1-naphthoic acid in 90% yield from 1-acetylnaphthalene[710], 5-indanecarboxylic acid in 75% yield from 5-acetylindane[712], and 6-carboxydehydroabietic acid in 70–80% yield from methyl 6-acetyldehydroabietate[713].

Treatment of methoxy-substituted ω-chloroacetophenones with pyridine hydrochloride affords a double transformation converting the chloroacetyl group into a pyridinioacetyl group while the methoxy groups are cleaved to hydroxy groups. Treatment of the resulting product with boiling aqueous sodium hydroxide effects degradation of the pyridinioacetyl group to a carboxyl group (equation 254)[714].



(254)

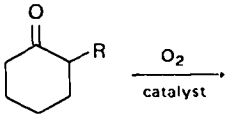
g. With oxygen, ozone, peroxide or air. Liquid-phase oxidation of a series of methyl alkyl and dialkyl ketones of the general formula shown in equation (255),

$$R^1CH_2COCH_2R^2 \xrightarrow[O_2]{120-140^\circ C} R^1COOH \qquad (255)$$

TABLE 33. Oxidation of α-alkylcyclohexanones using oxygen

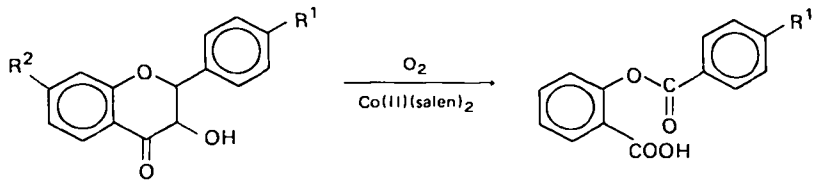
R	Catalyst	Yield (%)	Reference
Me	EtOH + NaOH	18	716
Me	KF	63	717
Me	LiF	14	717
Me	none	<1	717
Me	NaF	<5	717
Cyclohexyl	EtOH + NaOH	–	716
Cyclohexyl	KF	40	717

at 120–140° and 15 kg/cm^2 of oxygen pressure, produced the corresponding carboxylic acids in yields ranging from 72–83% via radical attack at the CH_2 group alpha to the carbonyl group[715]. Oxidation of α-alkyl-substituted cyclohexanones using oxygen has been accomplished using ethanolic sodium hydroxide[716] or fluorides of potassium, lithium, cesium or rubidium[717] as catalysts (Table 33) (equation 256). In a similar manner oxygen oxidation of 2-isopropyl-5-methylcyclohexanone afforded 3,7-dimethyl-6-oxooctanoic acid[716]. Cobalt or manganese acetate-catalysed oxygen oxidation of cyclooctanone or cyclododecanone in acetic acid gave suberic acid (65%) and 1,12-dodecanedioic acid, respectively[718].



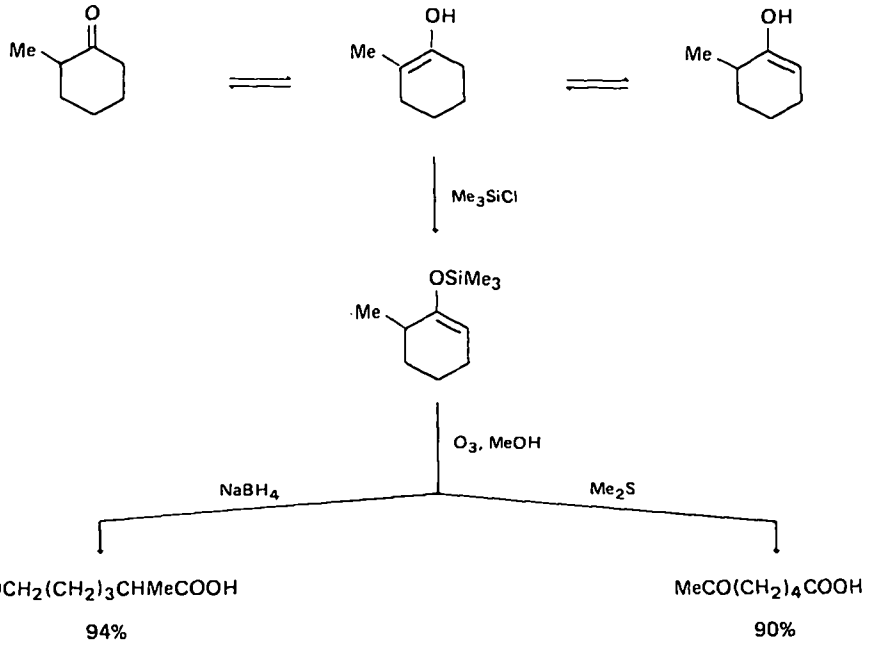
$$\xrightarrow{} \quad RCO(CH_2)_4COOH \qquad (256)$$

Recently, bis(salicylidene)ethylenediaminatocobalt(II) [Co(salen)$_2$] has been reported[719] to catalyse the oxygen oxidation of 3-hydroxyflavones in dimethylformamide or dimethylsulphoxide, but not in methanol, tetrahydrofuran or methylene chloride, giving rise to oxidative cleavage of the heterocyclic ring of the flavones affording the corresponding depsides in excellent yields (equation 257).

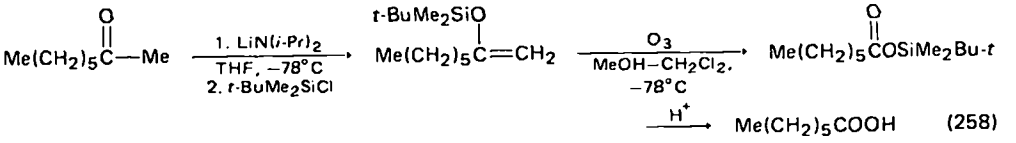


(257)

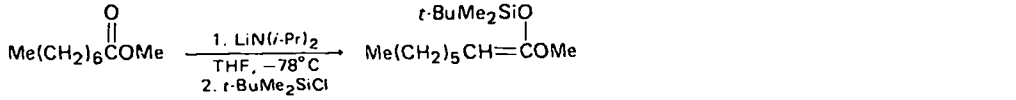
Although ozone is not a commonly used reagent for the oxidation of ketones *per se*, it has been used to oxidize ketone derivatives to carboxylic acids. Ozonolysis of silyoxyalkenes, which are generated from ketones by trapping the kinetic or thermodynamic enolate with a trialkylsilyl chloride or by trapping the kinetic enolate generated in the conjugate addition of organometallic reagents to enones, followed by a workup of the ozonolysis product with sodium borohydride affords hydroxy acids. If the ozonolysis product is worked up using dimethylsulphide then keto acids are obtained[720]. This overall two-step process (Scheme 5) of forming and cleaving the kinetic enolate provides a method of oxidatively cleaving an unsymmetrical ketone away from the more highly alkylated side of the molecule. This method has also been applied[720] to acyclic ketones as shown in equation (258). It has also been observed[720] that the oxidation of silylated ketone acetals

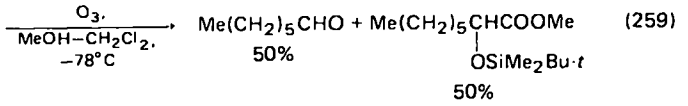


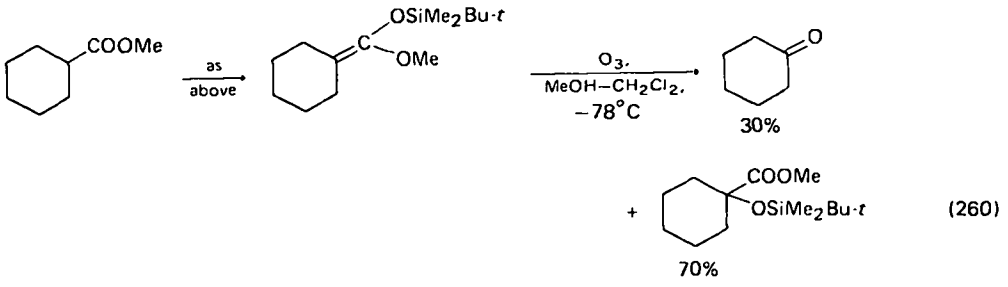
SCHEME 5.



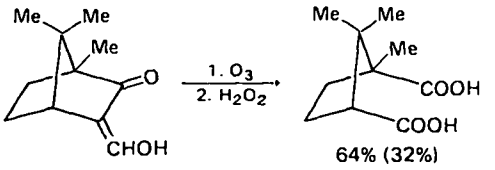
can lead to anomalous results (equations 259 and 260). A mechanism for this mode of reaction is presented[720].







Although oxidative ozonolysis of hydroxymethylene ketones leads to diacids these products are contaminated with large amounts of anhydrides. However if a basic hydrolysis step is included during the workup an improvement in the yields of the diacids formed is realized[721,722]. Examples of diacids prepared by this improved procedure are given in equations (261) and (262), with the yields in parentheses representing the results obtained without inclusion of the basic hydrolysis step.



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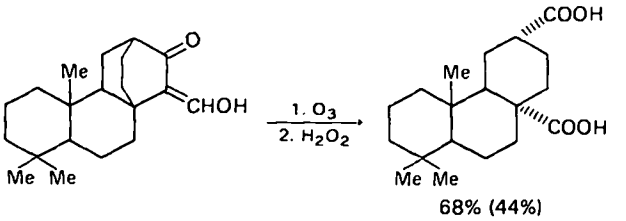
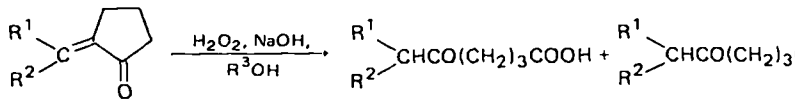


(262)

Conversions of keto steroids into carboxy steroids using ozone have also been reported[723].

Solutions of hydrogen peroxide containing a variety of catalysts have been used to prepare mono- and dicarboxylic acids from acyclic ketones. Using a solution of hydrogen peroxide in *t*-butyl alcohol containing 2 mole % of selenium dioxide at 80°C for two hours has effected oxidative ring-contractions of cycloheptanone, cyclohexanone and cyclopentanone to cyclohexane-, cyclopentane- and cyclobutanecarboxylic acids in 34, 32 and 23% yields, respectively[724]. With 30% hydrogen peroxide containing sodium hydroxide a variety of α,β-unsaturated carbonyl compounds have been converted to mono- and dicarboxylic acids as indicated in Table 34[725], while using the same oxidizing mixture in an alcohol converts a series of 2-alkylidenecyclopentanones into a mixture of 5-oxoalkanoic acids and their corresponding esters (equation 263)[726]. From this reaction the

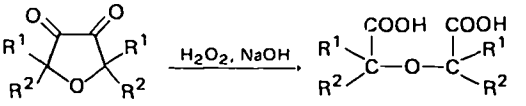


(263)

TABLE 34. Preparation of carboxylic acids from α,β-unsaturated carbonyl compounds using hydrogen peroxide

α,β-Unsaturated carbonyl compounds	Product	Yield (%)
2-Cyclohexen-1-one	Glutaric acid	72
1-Acetyl-1-cyclohexene	Adipic acid	67
Isophorone	3,3-Dimethyl-5-ketohexanoic acid	84
Pulegone	3-Methyladipic acid	60
Verbenone	Pinononic acid (1 : 1 *cis,trans* mixture)	85
Citral	2-Methyl-2-hepten-6-one	77
5,5-Dimethyl-1,3-cyclohexanedione	3,3-Dimethylglutaric acid	80

yields of acids are in the range of 25% while the yields of ester are in the range of 60%. A comparable reaction mixture has been reported[727] to effect the conversions shown in equations (264) and (265).



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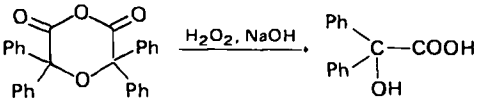
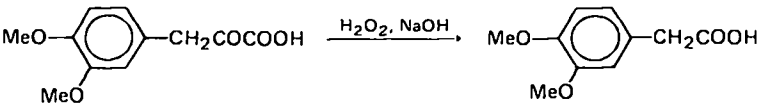


(265)

Hydrogen peroxide in the presence of alkali has also been used to prepare carboxylic acids from α-keto acids and α-keto esters. The preparation of 3,4-dimethoxyphenylacetic acid (equation 266)[728] and 9-fluorenecarboxylic acid (equation 267)[729] are typical of such reactions.



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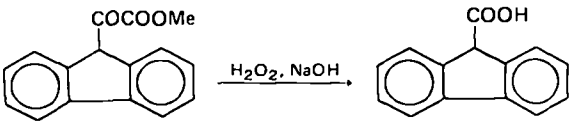


(267)

The application of cycloalkanone peroxides in the synthesis of various types of carboxylic acids has been reviewed[730]. An example of this type of reaction is illustrated by the preparation of 6-hydroxycaproic acid and adipic acid from cyclohexanone upon treatment with cyclohexanone hydroperoxide[731].

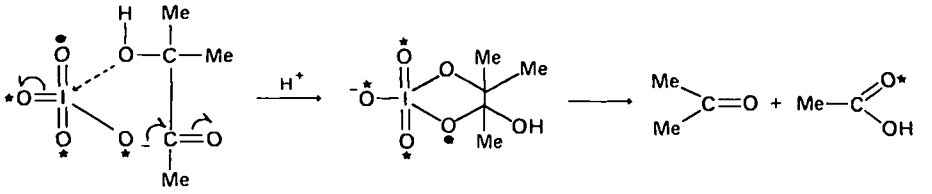
Aromatic carboxylic acids have also been prepared via air oxidation of alkyl aryl ketones in water and in the presence of a promoting agent such as copper(I) chloride[732]. Using this method benzoic, *o*- and *p*-toluic and 2-naphthoic acids have been prepared from acetophenone, *o*- and *p*-methylacetophenone and 2-acetonaphthalene, respectively.

h. With periodate. The use of periodate as an oxidizing agent has been reviewed at least seven times[325,733-738], the first review[733] being published in 1928, and the latest review[325] being published in 1974.

A variety of aliphatic, aromatic and alicyclic mono- and diketones have been oxidized by periodate to afford the corresponding carboxylic acids. A study[739] of the mechanism of periodate oxidation has been published using ^{18}O as a tracer in ^{18}O-labelled periodate. When this reagent was used in the oxidation of methylacetoin (3-hydroxy-3-methylbutan-2-one), acetone and acetic acid were the products isolated, and it was established that the oxygen of the acetone came from the hydroxyl group of the hydroxy ketone starting material and that the additional oxygen atom of the acetic acid came from the periodate according to the mechanism shown in equation (268)[740]. Other aliphatic ketones which have been treated with periodic acid or periodates and converted to their corresponding carboxylic acids are shown in Table 35.

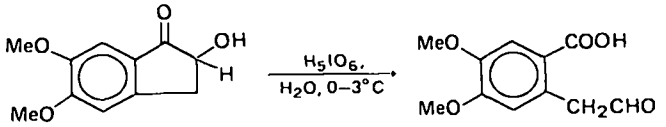
TABLE 35. Preparation of carboxylic acids from ketones using periodic acid or periodates

Ketone	Reagent	Product	Reference
Benzoin	$NaIO_4 + NaOH$	Benzilic acid	741
Benzoin	$NaIO_4 + H_2SO_4$	Benzoic acid	742
Acetoin	$NaIO_4 + H_2SO_4$	Acetic acid	742
Methylglyoxal	$NaIO_4 + H_2SO_4$	Formic acid + acetic acid	742
p-Toluoylphenylcarbinol	$NaIO_4 + H_2SO_4$	*p*-Toluic acid	742
Dihydroxyacetone	$NaIO_4 + H_2SO_4$	Glycollic acid	742
3,5-Dehydroxy-2-carboxybenzoyl methyl ketone (hydrate)	$NaIO_4 + H_2SO_4$	3,5-Dihydroxyphthalic acid	742
Benzfuroin	$NaIO_4 + H_2SO_4$	Pyromucic acid	742
3,5-Dihydroxy-2-carboxyphenyl-acetylcarbinol	$NaIO_4 + H_2SO_4$	6-Aldehydo-2,4-dihydroxybenzoic acid + acetic acid	742
2-Hydroxymethylenecyclohexanone	$NaIO_4$	Adipic acid	743



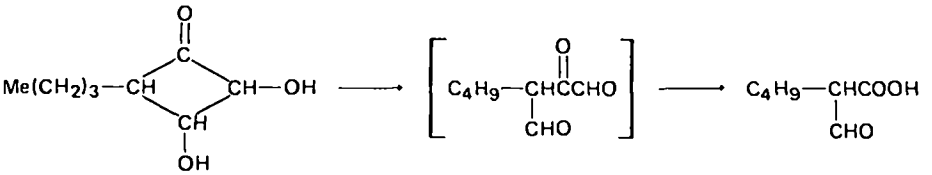
(268)

One of the largest classes of compounds which have been oxidized to acids using periodates and periodic acids are α-hydroxy cyclic ketones. Oxidation of 2-hydroxyindan-1-one derivatives with cold periodic acid produces *o*-carboxyphenylacetaldehydes in high yields[744], thus periodic acid oxidation of 2-hydroxy-5,6-dimethoxyindane-1-one in water at 0–3°C afforded 2-carboxy-4,5-dimethoxyphenylacetaldehyde in 90% yield (equation 269). Tetrahydroterrein, the reduction



(269)

product of terrein, has been reported[745] to produce its corresponding aldehydic acid upon treatment with periodic acid, probably via the intermediate ketoaldehyde (equation 270).



(270)

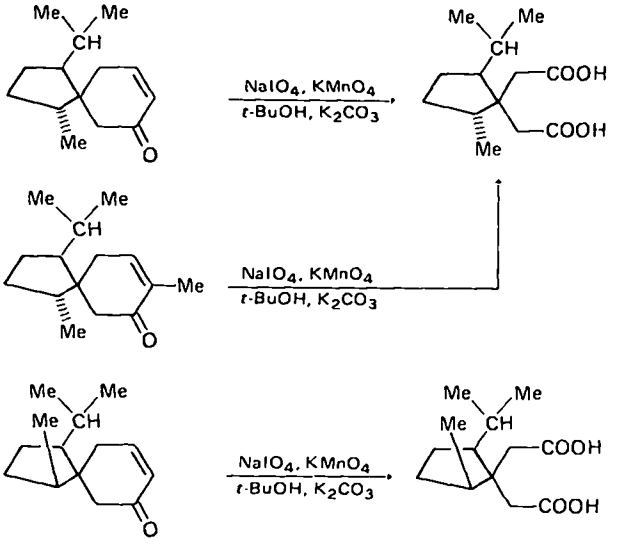
Both 1,2- and 1,3-diketones yield carboxylic acids upon periodate oxidation. For example, biacetyl(butane-2,3-dione) has been oxidized by basic solutions of ^{18}O-labelled periodate[739] affording acetic acid in which the additional oxygen atom of the acetic acid comes from the periodate. This oxidation was also performed using acidic periodate[742] and acetic acid was again obtained. Other diketones which have been converted to carboxylic acids using periodates[746]

TABLE 36. Conversion of diketones to acids using periodates

Diketone	Acid obtained	Yield (%)
1,3-Cyclohexanedione	Glutaric	86.5
5-Methyl-1,3-cyclohexanedione	3-Methylglutaric	90
5,5-Dimethyl-1,3-cyclohexanedione	3,3-Dimethylglutaric	92
1,3-Indandione	Succinic	–
1,3-Indandione	Phthalonic +	18.3
	phthalic	18.5
2-Methyl-1,3-cyclohexanedione	Acetic +	94
	glutaric	59
2-Ethyl-1,3-cyclohexanedione	Propionic +	90
	glutaric	68
2-Benzyl-1,3-cyclohexanedione	Phenylacetic +	85
	glutaric	73

include benzil which affords benzoic acid[742] and the cyclic 1,3-diketones[747] shown in Table 36. In addition, the reaction of periodate ion with the three acyclic 1,3-diketones, 2,4-pentanedione, 1-phenyl-1,3-butanedione and 1,3-diphenyl-1,3-propanedione, was observed to occur only very slowly, if at all[747]. These results and others led to the conclusion[747] that five- or six-membered cyclic 1,3-diketones which are unsubstituted on $C_{(2)}$ reduce four molar equivalents of periodate and afford one equivalent of carbon dioxide and one equivalent of a dibasic acid, while six-membered cyclic 1,3-diketones which are substituted on $C_{(2)}$ reduce three molar equivalents of periodate and afford one equivalent of a monobasic acid and one equivalent of a dibasic acid. Postulated reaction intermediates and the mechanism are also presented.

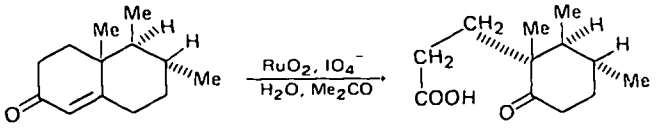
Reports of the use of periodate as a cooxidant in conjunction with a variety of other compounds for the oxidation of ketones to carboxylic acids have also appeared in the literature. Of these other materials, potassium permanganate (Lemieux–von Rudloff reagent) appears to be the most widely used. Although α,β-unsaturated keto steroids have been the most widely oxidized[556,748] class of compounds using this combination of reagents, the stereoisomeric spiro-[4.5]decanone derivatives shown in equations (271) and (272) have also been converted[749] to their corresponding dicarboxylic acids using mixtures of sodium periodate and potassium permanganate in *t*-butanol containing potassium carbonate.



(271)

(272)

Another material which is used with periodate as a cooxidant is ruthenium dioxide[497]. Reaction of sodium periodate and ruthenium dioxide generates ruthenium(VIII) oxide *in situ*, and addition of sodium periodate during the reaction regenerates the tetroxide. This reagent is useful for cleavage of conjugated and cross-conjugated steroidal ketones (equation 273)[497]. Thus, testosterone is

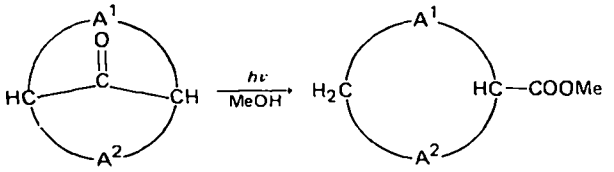


(273)

converted to its keto acid in 80% yield[497]. Using this reagent mixture to oxidize oestradiol diacetate affords[497] 3,17β-diacetoxy-9α-hydroxy-6-oxooestra-1,3,5(10)-triene in 40% yield via an interesting double allylic oxidation.

i. With light (photochemically). The light-induced formation of acids from cyclic ketones has been thoroughly reviewed[750] through 1963, and the information contained in this review will not be repeated.

By the reaction of cyclic ketones with ω,ω′-dihaloalkanes the carbonyl-bridged cycloalkanes shown in equation (274) are obtained[751], which upon photolysis in methanol afford the corresponding methyl cycloalkanecarboxylates.



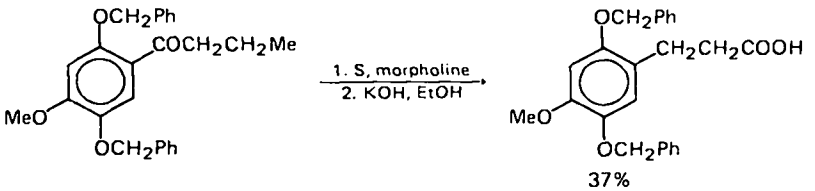
(274)

A^1	A^2	Yield (%)
$-(CH_2)_9-$	$-(CH_2)_4-$	73
$-(CH_2)_{10}-$	$-(CH_2)_3-$	55
$-(CH_2)_{10}-$	$-CH_2-CHMeCH_2-$	33

j. With sulphur (Willgerodt reaction). The Willgerodt reaction, which consists of the conversion of a straight- or branched-chain aryl alkyl ketone into an amide and/or the ammonium salt of an acid using ammonium polysulphide (equation 275), has been reviewed[752,753]. The carbonyl group of the product always occurs

$$ArCOCH_2Me \xrightarrow{(NH_4)_2S_x} ArCH_2CH_2COOH + \text{amide} \qquad (275)$$

at the end of the chain, and yields decrease sharply with increasing chain length. If sulphur and a dry primary or secondary amine are used as the reagents the reaction is called the Kindler modification[754] of the Willgerodt reaction and the products obtained in this case are alkylthioamides which can be hydrolysed to their corresponding acids. A more recent example[755] of this reaction is shown in equation (276).



37%

(276)

k. With miscellaneous reagents. Reaction of a variety of ketone hydrazones with lead tetraacetate has recently been reported[756-758] to effect good conversion to carboxylic acid esters. The extent of the conversion and the versatility of the reaction is demonstrated by the results shown in Table 37.

Preparation of substituted benzoylformic acids has recently been accomplished[759-761] by the potassium permanganate oxidation of the corresponding

TABLE 37. Oxidation of ketone hydrazones to esters using lead tetraacetate

Hydrazone of	Product	Yield (%)
3β-Hydroxylanostan-7-one	3β-Acetoxylanost-7-ene + 3β;7α-diacetoxylanostan	20 68
3β-Hydroxylanost-24-en-7-one	3β-Hydroxylanosta-7,24-diene + 3β-hydroxy-7α-acetoxylanost-24-ene	20 68
Benzophenone + dimethylacetylenedicarboxylate	3,4-Diphenylpyrazole-5-carboxylic acid	84
Dicyclohexyl ketone	Dicyclohexylmethyl acetate	46
Dicyclohexyldiazomethane	Dicyclohexylmethyl acetate	26
17β-Acetoxy-5α-androstan-3-one	5α-Androstan-3α,17β-diol diacetate + 5α-androstan-3β,17β-diol diacetate	32.4 19

substituted acetophenones in pyridine at 10°C (equation 277), while treatment of acetophenones in acidic methanol with thallium(III) nitrate affords[762] methyl phenylacetates via a simple one-step conversion (equation 278). Thallic ion in perchloric acid has also been used to effect[756] ring-contractions of cycloalkanones to cycloalkanecarboxylic acids. The contractions effected using this method are: cyclohexanone to cyclopentanecarboxylic acid, 3-methylcyclohexanone to 2-methylcyclopentanecarboxylic acid, 4-methylcyclohexanone to 3-methylcyclopentanecarboxylic acid and 2,2-dimethylcyclohexanone to 2,2-dimethylcyclopentanecarboxylic acid.

$$\mathrm{ArCOMe} \xrightarrow[C_5H_5N]{KMnO_4} \mathrm{ArCOCOOH} \qquad (277)$$

$$\mathrm{ArCOMe} \xrightarrow[HClO_4,\ MeOH]{Tl(NO_3)_3} \mathrm{ArCH_2COOMe} \qquad (278)$$

The transformation of an aromatic carboxylic ester into a chain-extended aromatic carboxylic ester containing additional functional groups has been reported[757] via an intermediate β-keto sulphoxide. Thus, condensation of esters with dimethylsulphoxide in basic solution gives the corresponding β-keto sulphoxides (equation 279), which upon treatment with a basic solution of bromine afford

$$\mathrm{ArCOOR} + \mathrm{Me_2SO} \xrightarrow{KOBu\text{-}t} \mathrm{ArCOCH_2SOMe} \qquad (279)$$

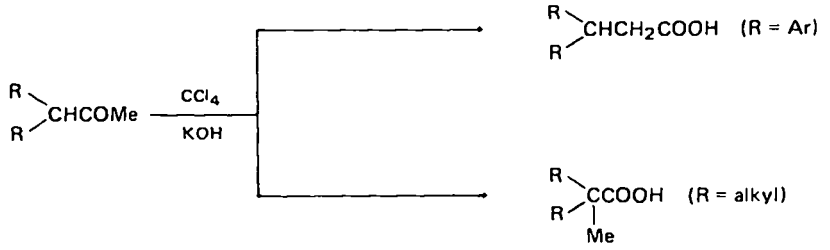
Ar	Yield (%)
Ph	88
p-MeC_6H_4	87
p-$MeOC_6H_4$	95
p-BrC_6H_4	79
α-$C_{10}H_7$	95
β-$C_{10}H_7$	91

$$ArCOCH_2SOMe \xrightarrow[base]{Br_2} ArCOCHBrSOMe \qquad (280)$$

$$ArCOCHBrSOMe \xrightarrow{ROH} ArCOCOOR \qquad (281)$$

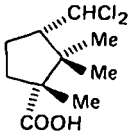
α-bromo-β-keto sulphoxides (equation 280). Treatment of these α-bromo-β-keto sulphoxides with alcohols affords the corresponding esters (equation 281).

Reaction of ketones containing α- but no α′-hydrogens with potassium hydroxide solutions of carbon tetrachloride results[758] in poly-α-chlorinated products which are subsequently cleaved via the haloform reaction to carboxylic acids. However, reaction of the same reagents with ketones containing α- and α′-hydrogens transforms them *in situ* into the carboxylic acids expected to be formed via the Favorskii reaction on the corresponding α-chloro ketones (equation 282) (Table 38)[758].



(282)

TABLE 38. Preparation of carboxylic acids from ketones using potassium hydroxide

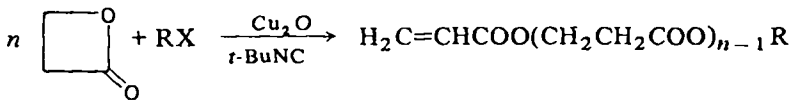
Ketones	Product	Yield (%)
Me_3CCOMe	Me_3CCOOH	80
Camphor		70
$Ph_2CHCOMe$	Ph_2CHCH_2COOH	70
$Me_2CHCOMe$	Me_3CCOOH + $Me_3CCOOCMe_3$	70 20–50

7. *Oxidation of Amines and Lactones*

Reaction of 3-hydroxyldialkylamines, which can be formed from a Mannich reaction[766], with sodium periodate[767] affords a number of cleavage products including carboxylic acids (equation 283). Similar reactions with 1-phenyl-2-piperidinoethane and 1-phenyl-2-morpholinoethane gave[767] phenylacetic acid in both cases.

$$PhCH(OH)CH_2CH_2NEt_2 \xrightarrow{NaIO_4} PhC(OH)CH_2COOH \qquad (283)$$

TABLE 39. Preparation of acrylates from β-propiolactone and alkyl halides



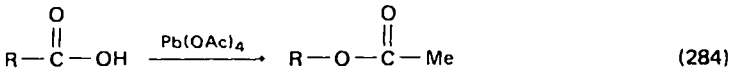
R	X	Yield (%)		
		$n = 1$	$n = 2$	$n = 3$
$MeOCCH_2-$	Cl	35	26	2
$n\text{-}C_4H_9-$	I	30	27	11
$s\text{-}C_4H_6-$	Br	9	29	11
$PhCH_2-$	Br	15	5	–
$CNCH_2-$	Cl	20	–	–

Heating β-propiolactone with alkyl halides in the presence of copper(I) oxide and *t*-butyl isocyanide as catalysts results[768] in the formation of an oligomer mixture of acrylates (Table 39).

8. *Oxidation of acids*

The interconversion of one acid into another acid or ester via oxidation has been accomplished using a variety of reagents.

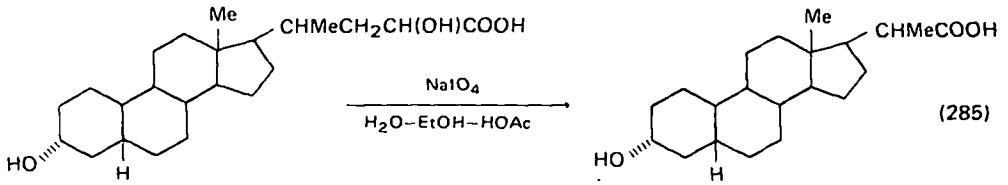
Oxidative decarboxylation of acids by lead tetraacetate[769] converts the original acid into an acetate ester under the conditions of the reaction (equation 284).



(284)

Using potassium permanganate in base converts[770] oleic acid into a mixture of 9-hydroxy-10-ketostearic and 10-hydroxy-9-ketostearic acids, while using the same reagent, elaidic acid is converted[770] into a mixture of the two hydroxyketo stearic acids mentioned above and 9,10-dihydroxystearic acid. With chromic acid in glacial acetic acid, 9-hydroxy-10-ketostearic acid is converted[770] into stearoxylic acid, while acidic potassium permanganate converts[770] nonanoic acid into a mixture of azelaic acids.

Periodate oxidation of α-hydroxy bile acids causes Barbier–Wieland degradation[771] into another acid. Thus, reaction of 3α,23-dihydroxycholanic acid in water–ethanol–acetic acid with sodium periodate affords norcholanic acid (equation 285)[772].



(285)

Oxidation via anodic electrolysis has also been found[773] to convert acids into esters, since electrolysis of mono- and diphenylacetic acids in acetic acid solution affords benzyl and diphenylmethyl acetates both in about 40% yield.

H. Acids by Cleavage Reactions

Carboxylic acids are obtained as products from the cleavage of a variety of other functional groups using a variety of reagents. The most common functional groups which produce acids upon cleavage are ethers and ketones, and a discussion of the cleavage reactions these groups undergo will be presented in this section.

1. Of ethers

The cleavage reactions of ethers, many of which lead to carboxylic acids, were reviewed by Burwell[774] in 1954. More recently however, aqueous bromine has been reported[775] to react with a wide variety of aliphatic ethers at 25°C via an oxidative cleavage mechanism to afford carboxylic acids. In addition to a determination of the products and yields which are shown in Table 40, this report[775] also investigated the determination of the rate law and the pH-rate profile for this cleavage.

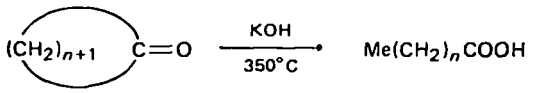
TABLE 40. Preparation of acids from ethers using bromine

Ether	Acid product	Yield (%)
Diethyl	Acetic	100
Dipropyl	Propionic +	95
	α-bromopropionic	5
Dibenzyl	Benzoic +	55
	4-bromobenzoic	45
4-Nitrobenzyl methyl	4-Nitrobenzoic	68

Another recent approach to the production of carboxylic acids via cleavage reactions involves the alkali fusion of long-chain unsaturated fatty acids[776–779], keto and hydroxy acids[776–780], acids with vicinal oxygen functions[776,777], and epoxy and alkoxy acids[781]. This latter approach affords a series of mono- and dicarboxylic acids from several different starting ethers. Thus, potassium hydroxide fusion of *cis*- and *trans*-9,10-epoxyoctadecanoic acids and *threo*- and *erythro*-9,10-dihydroxyoctadecanoic acids at 300°C for one hour affords octanoic, nonanoic and nonanedioic acids in roughly equimolar amounts[781]. Other acids cleaved[781] by alkali fusion include: 10,11-epoxyundecanoic acid, *cis*-9,10-*cis*-12,13-diepoxyoctadecanoic acid, 9,10,12,13-tetrahydroxyoctadecanoic acid, 9,12-dioxooctodec-10-enoic acid, 10,11-epoxy-12-oxooctadecanoic acid and a series of 11-alkoxyundecanoic acids.

2. Of ketones

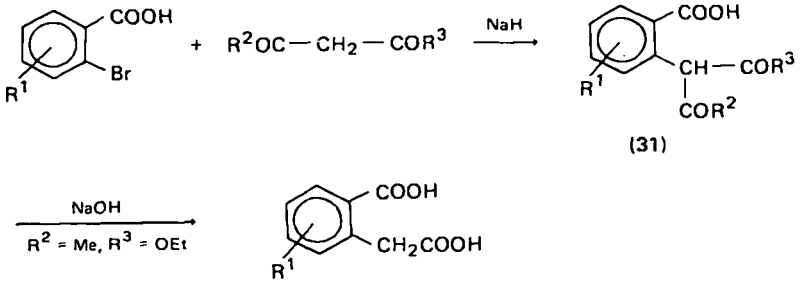
Cleavage of ketones to produce acids and/or esters is usually accomplished with strong bases such as *t*-butoxide; however several examples have been reported where milder hydroxide bases have been used. Potassium hydroxide in olefin-free petroleum oil at 350°C has been used to effect ring-opening of cyclic ketones affording monocarboxylic acids (equation 286)[782]. The reactions were performed on ketones with $n = 4$ to $n = 10$ and the yields of acid increased rapidly from $n = 4$, where practically no ring-opening was observed, to $n = 10$ where a 55% yield was achieved.



(286)

Treatment of 2,2'-sebacoyldicyclohexanone with an ethanolic solution of sodium hydroxide affords disodium 7,16-diketodocosanedioate which upon reaction with hydrazine hydrate and potassium hydroxide in triethanolamine affords a 69–72% yield of docosanedioic acid[783].

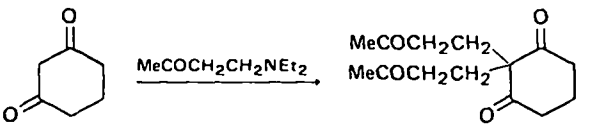
Reaction of a variety of substituted 2-bromobenzoic acids with β-keto esters in the presence of sodium hydroxide at 60–80°C using copper bromide as a catalyst affords[784] the corresponding α-acylhomophthalic acid half-esters (31) which upon hydrolysis with 2 N sodium hydroxide at room temperature produce[784] the substituted homophthalic acids (32) shown in equation (287).



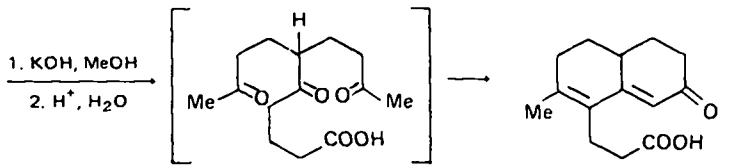
(287)

			Yield (%)	
R^1	R^2	R^3	31	32
H	Me	Me	91	
H	Me	OEt	96	92
H	OEt	OEt	92	
H	Ph	OEt	98	
4-Me	Me	Me	82	
4-Me	Me	OEt	99	88
4-Me	OEt	OEt	90	
4-NO_2	Me	Me	91	
4-NO_2	Me	OEt	98	90
4-NO_2	OEt	OEt	88	
5-MeO	Me	OEt	98	91
4,5-Di-MeO	OEt	OEt	92	
3,4,5-Tri-MeO	Me	Me	84	
3,4,5-Tri-MeO	OEt	OEt	84	

An interesting series of reactions has been reported[785] to occur during the Robinson–Mannich annelation of cyclohexane-1,3-dione. Reaction of cyclohexane-1,3-dione with an equivalent amount of 1-diethylamino-3-butanone in refluxing benzene in the presence of pyridine, followed by acidification, affords β(2-methyl-7-oxo-3,4,4a,5,6,7-hexahydronaphthalene-1)propanoic acid in 45–50% yield (equation 288). However, when two equivalents of 1-diethylamino-3-butanone are used, the yield of the substituted propanoic acid is increased to 90–95%. This same

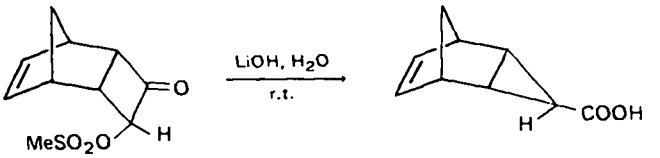


(288)



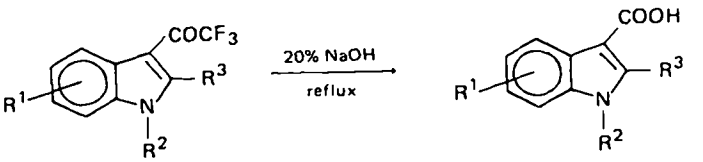
high yield of product is realized if the bis-adduct intermediate is hydrolysed via alkaline cleavage or by simply refluxing with diethylamine in benzene. Surprisingly, when annelation of cyclohexane-1,3-dione was carried out with butenone in the presence of Triton-B a different acid, β-(2-methyl-6-oxocyclohexene-1)propanoic acid, was obtained[785].

Aqueous lithium hydroxide at room temperature has been used to cleave the tricyclomethanesulphonic acid ester shown in equation (289) to afford[786] *endo-syn*-tricyclo[3.2.1.$0^{2,4}$]oct-6-en-3-carboxylic acid in 68% yield, formed by a four-carbon to three-carbon ring contraction. A 10% yield of the corresponding *endo-anti* carboxylic acid was also obtained.



(289)

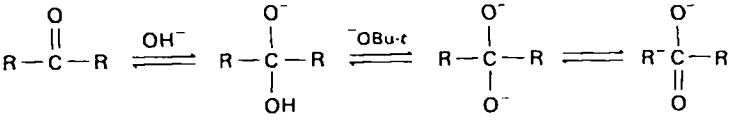
Hydroxy bases such as sodium hydroxide have also been used in the heterocycle field to cleave substituted 3-indolytrifluoromethyl ketones to substituted indol-3-carboxylic acids (equation 290)[787,788].



(290)

Since the original work of Gassman and coworkers[789,790] has been published, the cleavage of non-enolizable ketones with strong bases has received considerable attention[791-804]. Unlike the Haller–Bauer reaction[805], which involves the cleavage of ketones by sodium amide in refluxing benzene, toluene or xylene and yields amide and hydrocarbon moieties as products, the procedure of Gassman, which utilizes a 10 : 3 ratio of potassium *t*-butoxide–water mixture in aprotic solvents, such as ether (solvent of choice), dimethyl sulphoxide, glyme, hexamethylphosphoramide or hexane, affords carboxylic acids as products after only a few hours reaction time at room temperature. In addition, the stereochemistry of these reactions is such[790] that the acid function undergoes only a small amount of epimerization. The mechanism of cleavage of non-enolizable ketones with this

reagent mixture has been thoroughly investigated[790] and appears to involve initial addition of hydroxide ion to the carbonyl group followed by *t*-butoxide abstraction of a proton and cleavage of the resulting dianion (equation 291).

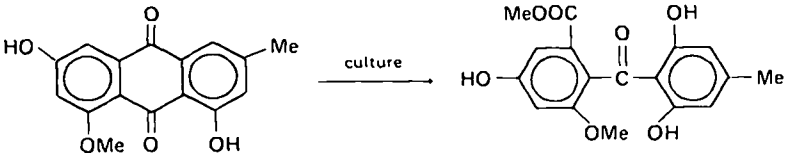


(291)

The extent to which this reaction has found synthetic usefulness for non-enolizable as well as for certain enolizable ketones, can be seen from the results in Table 41 which have been published on a wide range of systems by a variety of authors. A recent observation[806], which may be explained by a similar mechanism as that proposed by Gassman, is the conversion of benzophenone to benzoic acid using potassium hydride in THF–water solutions.

Hoffman and Cram[807,808] have published a rather complete study of the stereochemical reaction course of the base-catalysed cleavage of optically pure (+)-(*R*)-2-methyl-2-phenylcyclopentanone, and have found that in a variety of solvents (+)-(*S*)-5-phenylhexanoic acid was formed in 6–43% yield, with varying amounts of retention of configuration. Thus, in *t*-butyl alcohol–potassium *t*-butoxide about 61% net retention was observed, in dimethyl sulphoxide–*t*-butyl alcohol–potassium *t*-butoxide about 1% net retention and in diethylene glycol–potassium diethylene glycoxide approximately 27% net retention. To help establish the mechanism proposed[808] cleavage of (+)-(*R*)-5,5-dideuterio-2-methyl-2-phenyl-cyclopentanone in *t*-butyl alcohol–*O*-d-potassium *t*-butoxide was also investigated. This reaction gave the same hexanoic acid product with 62% net retention but which contained only 71% of one atom of deuterium at the methine carbon indicating that the carbanion intermediate was probably 'captured' by protons donated by the methyl groups of the medium.

A very interesting biodegradation of questin has been reported[809] in which the addition of questin to a 48-hour shake-flask culture of *Aspergillus terreus* (chlorine-free, Czapek–Dox medium), followed by further culture growth at 25°C for 25 hours, afforded sulochrin (equation 292). Using ^{14}C-labelled questin helped to



(292)

establish the mechanism for this biodegradative ketone cleavage, which appears to involve formation of the benzophenone from two distinct units each separately derived from acetate and malonate. The same transformation using *penicillium frequentans* has also been reported[810].

3. *Of miscellaneous functional groups*

Although ethers and ketones have been the two most common classes of compounds cleaved to produce acids and esters, other functional groups have also been reported to lead to acids under various cleavage conditions. Steroid alcohols have undergone fusion with potassium hydroxide[811] to afford acids, while pyrolysis of ethyl acrylate at 590°C has been reported[812] to lead to a 68–75% yield of acrylic acid.

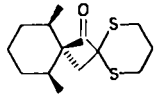
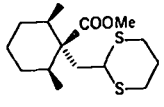
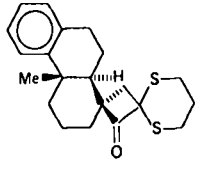
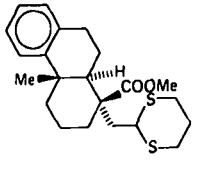
TABLE 41. Cleavage of non-enolizable and enolizable ketones

Starting ketone	System[a]	Product	Yield (%)	Reference
Nortricyclanone	A	*cis*- and *trans*-Bicyclo[3.1.0]hexane-3-carboxylic acid	65	789
Benzophenone	Varied	Benzoic acid	75–91	790–793
7-Ketonorbornene	A	Cyclohexene-4-carboxylic-acid +	32	790
		cyclohexene-1-carboxylic acid	18	
Dehydronorcamphor	A	Cyclopentene-4-acetic acid	80	790
Camphenilone	A	Camphoceenic acid	9	790
Dehydronorcamphor	B	Cyclopentene-4-acetic acid	19	794
Fenchone	C	No cleavage	–	790
Fluorenone	C	Biphenyl-2-carboxylic acid	90	790, 792
Phenyl triphenylmethyl ketone	A	Benzoic acid	100	790
Xanthone	C	2-Phenoxybenzoic acid	64	792
2-Chlorobenzophenone	C	Benzoic acid +	92	792
		2-chlorobenzoic acid	90	
3-Chlorobenzophenone	C	Benzoic acid +	93	792
		3-chlorobenzoic acid	91	
4-Chlorobenzophenone	C	Benzoic acid +	79	792
		4-chlorobenzoic acid	21	
2-Carboxybenzophenone	C	Benzoic acid +		
		phthalic acid	90	792
4-Carboxybenzophenone	C	Benzoic acid +		
		terephthalic acid	85	792
4-Phenylbenzophenone	C	Benzoic acid +		
		4-phenylbenzoic acid	92	792
2-Methylbenzophenone	C	Benzoic acid +		
		2-methylbenzoic acid	59	792
3-Methylbenzophenone	C	Benzoic acid +	18	792
		3-methylbenzoic acid	90	
4-Methylbenzophenone	C	Benzoic acid +		
		4-methylbenzoic acid	73	792
2-Methoxybenzophenone	C	Benzoic acid +	92	792
		2-methoxybenzoic acid	99	
3-Methoxybenzophenone	C	Benzoic acid +		
		3-methoxybenzoic acid	90	792
4-Methoxybenzophenone	C	Benzoic acid +		
		4-methoxybenzoic acid	55	792
2-Chloro-4'-phenylbenzophenone	C	Biphenyl-4-carboxylic acid	91	795
2-Chloro-3',4'-dimethylbenzophenone	C	3,4-Dimethylbenzoic acid	77	795

TABLE 41—*continued*

Starting ketone	System[a]	Product	Yield (%)	Reference
2-Chloro-2',4',6'-trimethylbenzophenone	C	2,4,6-Trimethylbenzoic acid	76	795
2-Chloro-3',4'-dimethoxybenzophenone	C	3,4-Dimethoxybenzoic acid	85	795
2-Chloro-2',4'-dimethoxybenzophenone	C	2,4-Dimethoxybenzoic acid	69	795
2-(2-Chlorobenzoyl)thiophen	C	Thiophen-2-carboxylic acid	–	795
2-(2,6-Dichlorobenzoyl)thiophen	C	Thiophen-2-carboxylic acid	72	795
9,10-Anthraquinone	D	Benzoic acid +	78	796
		phthalic acid	20	
Tetracen-5,12-quinone	D	Benzoic acid +	52	796
		β-naphthalenecarboxylic acid	42	
Dibenz[a,c]anthraquinone	D	Benzoic acid +	17	796
		phthalic acid +	51	
		9-phenanthrenecarboxylic acid	16	
Tetrabenz[a,c;h,j] anthraquinone-9-10	D	9-Phenanthrenecarboxylic acid +	44	796
		9,10-phenanthrenedicarboxylic acid	4	
9,10-Anthraquinone-β-carboxylic acid	D	Benzoic acid +	35	796
		phthalic acid +	16	
		iso- and terephthalic acid +	39	
		trimellitic acid	17	
Anthranthrone	D	1,1'-Dinaphthyl-2,2'-dicarboxylic acid +	4	796
		1,1'-dinaphthyl-8,8'-dicarboxylic acid	4	
1,2-Dibenzoylbenzene	E	Benzoic acid +	99	791
		phthalic acid	1	
1,3-Dibenzoylbenzene	E	Benzoic acid +	99	791
		isophthalic acid	1	
1,4-Dibenzoylbenzene	E	Benzoic acid +	99	791
		terephthalic acid	1	
4-Benzoylbiphenyl	E	Benzoic acid	50	791
1-Benzoylnaphthalene	E	Benzoic acid +	92	791
		α-naphthoic acid	8	
2-Benzoylnaphthalene	E	Benzoic acid +	91	791
		β-naphthoic acid	9	
6-Benzoylchrysene	E	Benzoic acid	45	791
1-Benzoylpyrene	E	Benzoic acid	40	791
1,3,6,8-Tetrabenzoylpyrene	E	Benzoic acid	84	791
1-(Naphthoyl-1)naphthalene	E	α-Naphthoic acid	50	791
2-(Naphthoyl-1)naphthalene	E	α-Naphthoic acid +	22	791
		β-naphthoic acid	29	
1-(Naphthoyl-1)pyrene	E	α-Naphthoic acid	44	791

TABLE 41—*continued*

Starting ketone	System[a]	Product	Yield (%)	Reference
2,6-Di(naphthoyl-1)-naphthalene	E	2,6-Naphthalene dicarboxylic acid +	45	791
		α-naphthoic acid +	3	
		β-naphthoic acid	1	
Pivalophenone	E	Pivalic acid	50	791
Acetophenone	E	Benzoic acid	60	791
(2-Chlorobenzyl)ferrocene	C	(2-Carboxy)ferrocene	98	797
(2-Chlorobenzoyl)cyclopentadienylmanganese tricarbonyl	C	(2-Carboxy)cyclopentadienylmanganese tricarbonyl	87	797
2,3-Dihydro-1-benzoxepin-5-on-4-spirocyclopentane	C	Salicylic acid	89	798
2,2-(Propane-1,3-dithio)cyclohexanone	F or G	6,6-(Propane-1,3-dithio)hexanoic acid	93	799–801
2,2-(Propane-1,3-dithio)cycloheptanone	F or G	7,7-(Propane-1,3-dithio)heptanoic acid	95	799–801
2,2-(Propane-1,3-dithio)cyclooctanone	F or G	8,8-(Propane-1,3-dithio)octanoic acid	89	799–801
2,2-(Propane-1,3-dithio)-4-cyclohepten-1-one	F or G	(Z)-7,7-(Propane-1,3-dithio)-4-heptanoic acid	93	799–801
3,3-(Propane-1,3-dithio)-10-methoxymethyl-*trans*-2-decalone	F or G	1-[2,2-(Propane-1,3-dithio)ethyl]-*cis*-1-methoxymethylcyclohex-2-yl acetic acid	92	799–801
3,3-(Propane-1,3-dithio)-1,1-dimethyl-*trans*-2-decalone	F or G	No reaction	–	799–801
3,3-(Propane-1,3-dithio)-10-methyl-9-decen-2-one	F or G	No cleavage products	–	799–801
2-Thiophenylcyclohexanone	G	No reaction	–	801
2-Methyl-2-thiophenylcyclohexanone	G	No reaction	–	801
2,2-Bis(thiophenyl)cyclohexanone	G	6,6-Bis-thiophenylhexanoic acid	66	801
2,2-Dibromo-4-methyl-4-hexylcyclobutanone	H	Methyl-2-(2,2-dibromoethyl)-2-methyloctanoate	90	802
2,2-Dibromo-1-cyclobutanone-4-spirocyclohexane	H	1-(2,2-Dibromoethyl)-1-carbomethoxycyclohexane	97	802
2,2-(Propane-1,3-dithio)cyclobutanone-4-spiro(1-tetralone)	H	1-[2,2-(Propane-1,3-dithio)]ethyl-1-carbomethoxytetralone	60	803
2,2-(Propane-1,3-dithio)-4-(4-cyclohexenyl)cyclobutanone	I	2-(4-Cyclohexenyl)-4,4-(propane-1,3-dithio)butanoic acid	–	803
	H		–	803
	H		100	803

[a] A = KOBu-*t* + DMSO + H_2O, B = KOBu-*t* + *t*-BuOH, C = KOBu-*t* + glyme + H_2O, D = KOBu-*t* + dioxane + H_2O, E = KOBu-*t* + anisol + H_2O, F = NaOBu-*t* + NaOH + *t*-BuOH + ether, G = KOH + *t*-BuOH + H_2O, H = NaOMe + MeOH and I = NaOH + H_2O.

I. Acids by Rearrangements

In addition to the well-known rearrangement reactions a few novel and interesting rearrangements have been used to prepare acids and esters. This section will include a discussion of all types of rearrangements which have been used to prepare acids and/or esters.

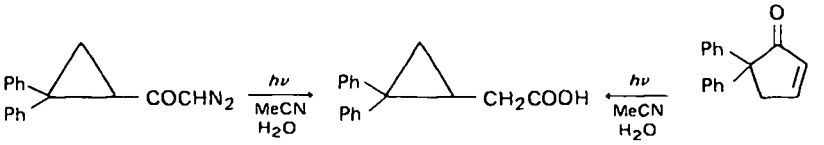
1. Arndt–Eistert and Wolff Rearrangements

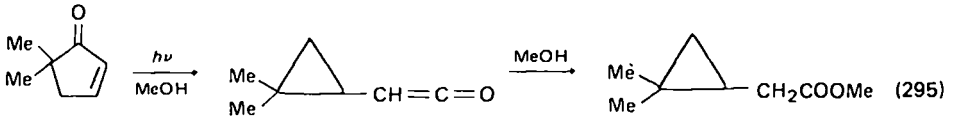
This rearrangement, which has been reviewed several times, beginning in 1941 by Eistert[813,814] by Bachmann and Struve[815] in 1942, by Eistert[816] again in 1948 and in 1964 by Weygand and Bestmann[817], involves the transformation of a carboxylic acid into its next higher homologue via a diazo ketone intermediate. The Wolff rearrangement, which accompanies the decomposition of the diazo ketone intermediate, is an integral step in any overall Arndt–Eistert synthesis.

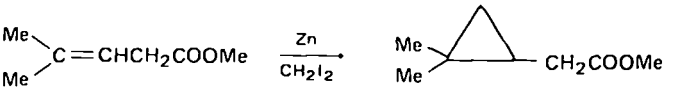
Several methods have been reported to prepare the intermediate diazo ketone required for this rearrangement, the most common method being treatment of an acid chloride with diazomethane or a substituted diazomethane, as shown in equation (293) for the preparation of 2-phenylpropionic acid[818]. A similarly

$$\mathrm{PhCOCl} \xrightarrow[\text{2. } Ag_2O,\ PhNH_2\text{; 3. acid hydrolysis}]{\text{1. } MeCHN_2\text{, ether}} \mathrm{PhCHMeCOOH} \qquad (293)$$

prepared diazo ketone was used in the preparation of 2,2-diphenylcyclopropaneacetic acid[819] via a photochemical Wolff rearrangement. This acid was also prepared[819] by photoisomerization of 5,5-diphenylcyclopentenone (equation 294). Photoisomerization of 5,5-dimethylcyclopent-2-enone[819] in the presence of methanol afforded the methyl ester of 2,2-dimethylcyclopropaneacetic acid (equation 295). The photochemical preparation of both the diphenyl-substituted acid and the dimethyl-substituted ester can be viewed as proceeding via a ketene in a reverse of the general vinylcyclopropane to cyclopentene rearrangement. Independent synthesis[819] of the dimethyl-substituted ester was accomplished by treatment of the methyl ester of 4-methyl-3-pentenoic acid with zinc and methylene iodide (equation 296).

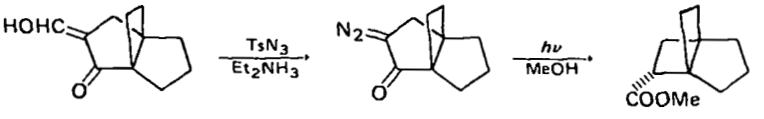




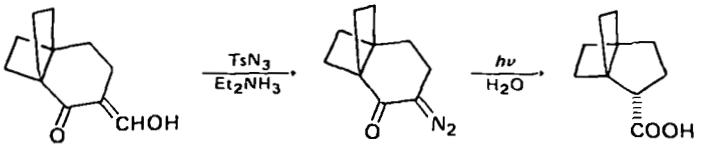


Another method used to prepare the required intermediate diazo ketone is illustrated by the reaction of 3-hydroxymethylene-2-oxo[3.3.2]propellane

(equation 297)[820,821] or 3-hydroxymethylene-2-oxo[4.2.2]propellane (equation 298)[820,821] with tosyl azide and diethylamine. These resultant diazo ketones were observed[821] to undergo ring-contraction via a photochemical Wolff rearrangement in methanol to give 65% yield of a mixture of epimeric 2-carboxy[3.2.2]propellane monomethyl esters or in aqueous dioxane to give 2-carboxy[3.2.2]propellane in 63% yield, respectively.

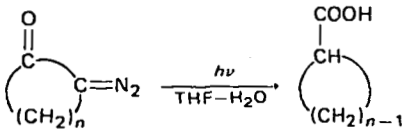


(297)

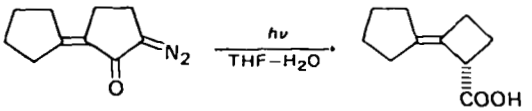


(298)

Similar ring-contractions have also been observed by Regitz and Ruter[822] upon photolysis of α-diazocyclic ketones in aqueous tetrahydrofuran (THF), producing cyclic acids (equations 299 and 300).

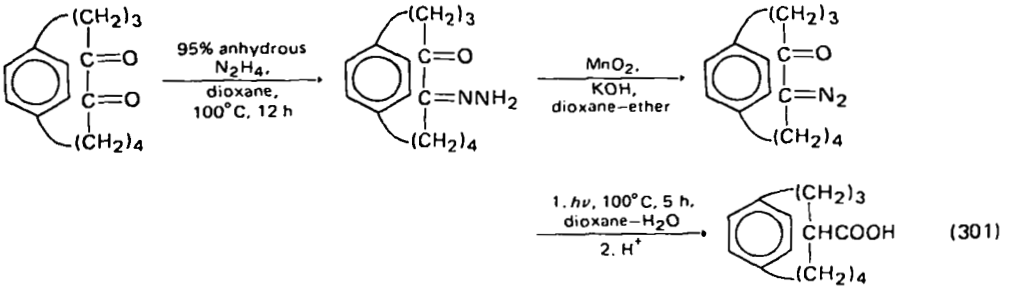


(299)



(300)

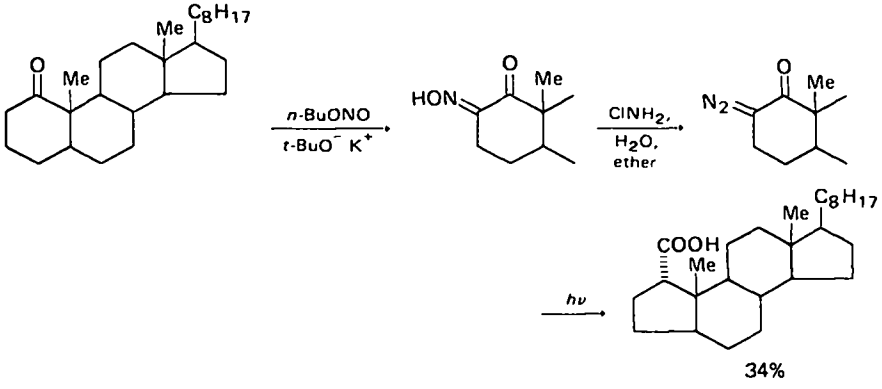
Diazo ketones of paracyclophanes have also been observed[823] to undergo ring-contractions during photochemical Wolff rearrangements to produce carboxylic acids, albeit in 25% yield. In this case[823] the required diazo ketone was prepared by base-catalysed manganese dioxide oxidation of 4,5-diketo-[9]-paracyclophane monohydrazone (equation 301).



(301)

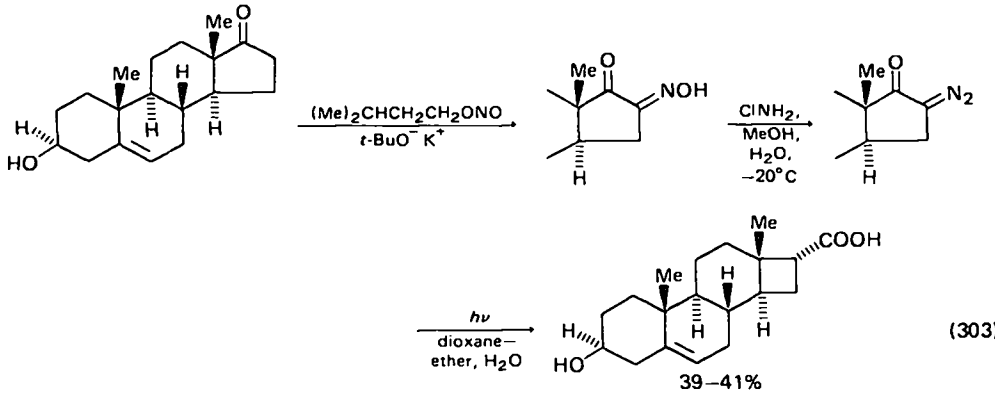
Ring-contractions producing carboxylic acids have also been reported in more complicated steroid systems. In each case the required diazo ketone has been

produced from an intermediate oxime by reaction with chloramine followed by a photochemical Wolff rearrangement (equations 302–304)[824-826].



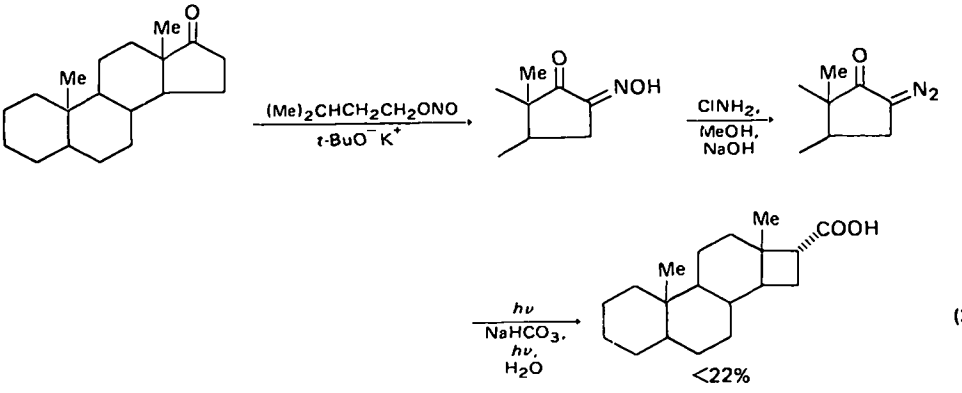
(302)

34%



(303)

39–41%

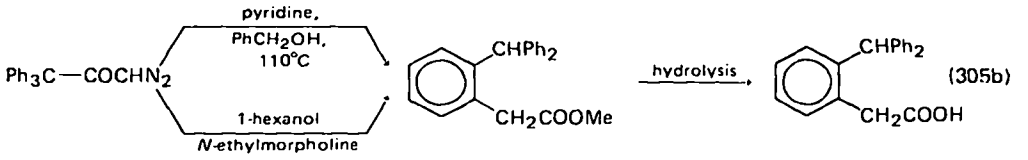


(304)

<22%

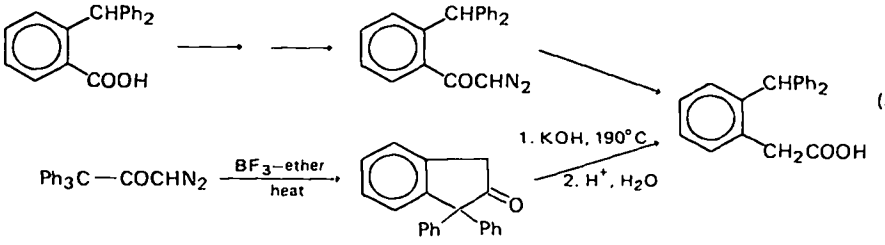
Even with the use of improved procedures[827-829] for the Wolff rearrangement of the intermediate diazo ketones, rearrangements have been reported[830] which do not proceed as expected but give abnormal acid derivatives which are isomeric with the expected product. Such a result was observed[830] upon heating triphenylacetyldiazomethane obtained by reaction of triphenylacetyl chloride with diazomethane (equation 305). Establishment of the structure of this product was accomplished by

$$Ph_3C{-}COCl + CH_2N_2 \longrightarrow Ph_3C{-}COCHN_2 \quad (305a)$$

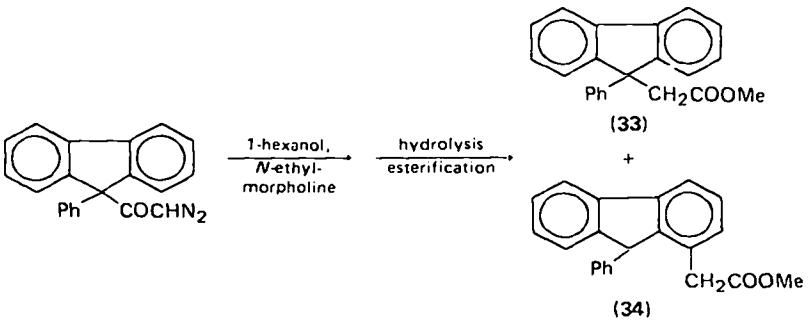


(305b)

two different independent syntheses[830], starting from triphenylmethane-*o*-carboxylic acid and 1,1-diphenyl-2-indanone, respectively (equation 306). In an attempt[830] to prove that this product was obtained because of steric interference with the normal Wolff rearrangement, 9-phenylflourene-9-carboxyldiazomethane was treated under similar conditions, to afford a 2 : 1 ratio of normal rearranged ester (33) to abnormal rearranged ester (34) (equation 307).

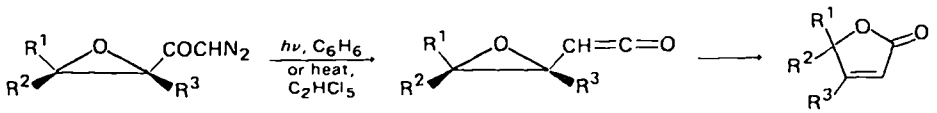


(306)



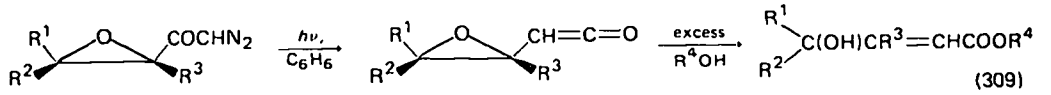
(307)

In addition to steric effects leading to abnormal products in the Wolff rearrangement, differences in reaction conditions can also lead to unexpected products during rearrangement as observed by Zwanenburg and coworkers[831]. Whereas photolysis of substituted α,β-epoxydiazomethyl ketones in benzene or simple reflux in pentachloroethane leads to intermediate epoxyketene formation and then to lactones (equation 308), photolysis in benzene in the presence of a ten-fold molar



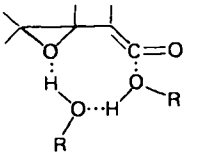
(308)

excess of methanol or ethanol leads to intermediate epoxyketene formation then to γ-hydroxy-α,β-unsaturated esters during rearrangement (equation 309)[831,832]. The interesting mechanism proposed[831] to explain these results involves spontaneous alcoholysis of the intermediate ketene via a cyclic transition state (35) involving



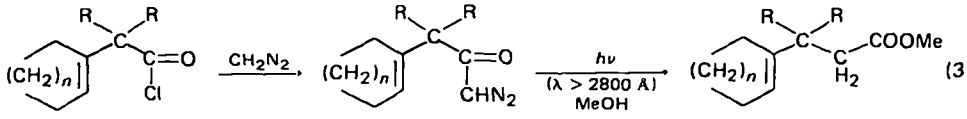
(309)

two associated alcohol molecules, one acting as a nucleophile on the ketene carbonyl carbon atom and the other serving as a proton source for the epoxide opening.

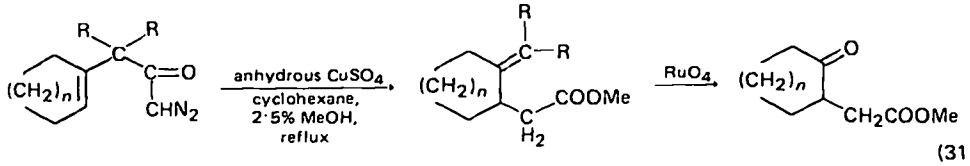


(35)

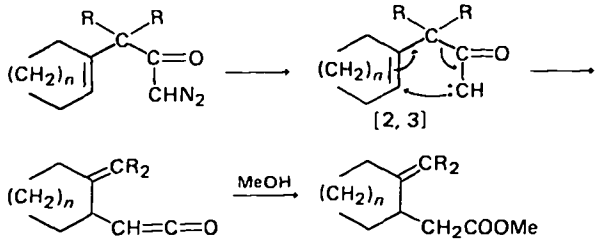
Other examples of unexpected products arising during the Wolff rearrangement are illustrated by the results of Smith[833], who found that photochemical rearrangement of unsaturated diazo ketones leads to the expected chain-lengthened ester (equation 310), while reflux in the presence of a copper sulphate catalyst generates, via skeletal rearrangement, a new γ,δ-unsaturated ester (equation 311). These products may be explained via a vinylogous Wolff-type [2,3]-sigmatropic rearrangement (equation 312).



(310)

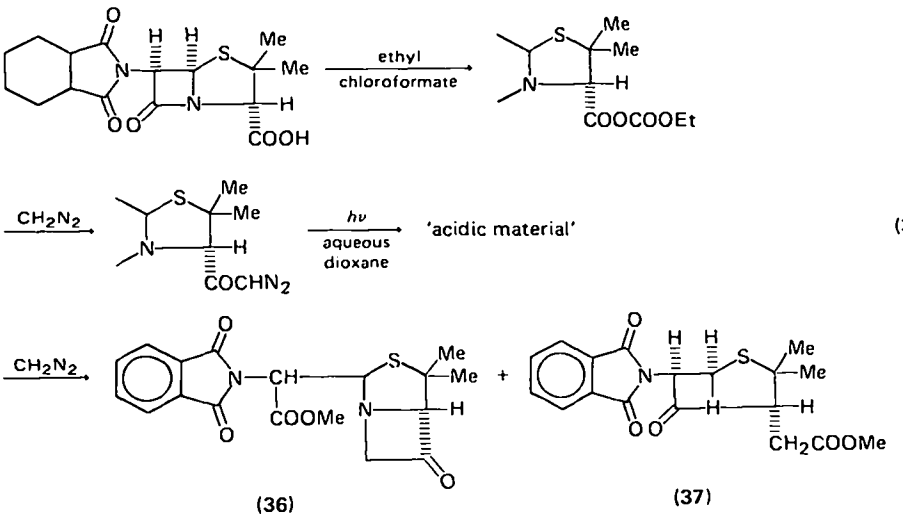


(311)



(312)

Arndt–Eistert reactions have also been applied to molecules related to penicillins such as the trimethylamine salt of 6-β-phthalimidopenicillanic acid[834]. In this case the intermediate diazo ketone, prepared by reaction of a mixed anhydride with diazomethane, upon photolysis afforded an 'acidic material', which upon esterification with diazomethane afforded 27% of methyl(α*R*, 2*R*, 5*S*)-α-(4,4-dimethyl-6-oxo-1-aza-3-thiabicyclo[3.2.0]hept-2-yl)-α-phthalimidoacetate (36) and 34% of methyl-6β-phthalimidohomopenicillanate (37).



(313)

(36) (37)

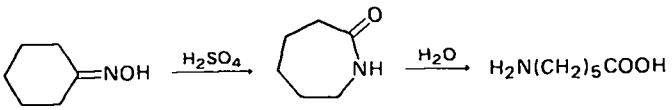
Application of the Arndt–Eistert reaction to 3-*o*-carborane derivatives[835] has shown that the Wolff rearrangement proceeds through boron–carbon bond cleavage and migration of the electron-rich 3-*o*-carboranyl group to the electron-deficient carbon centre to produce a carboranyl ketene, which upon hydrolysis affords 3-*o*-carborane-3-yl acetic acid. Production of the intermediate diazo ketone in these compounds was accomplished by treatment of the 3-*o*-carborane carboxylic acid chloride with diazomethane, while the standard silver oxide-catalysed decomposition of the diazo ketene was utilized to effect the Wolff rearrangement. Proof of structure of the 3-*o*-carborane-3-yl acetic acid obtained via this rearrangement was accomplished by an independent synthesis[835].

2. *Beckmann rearrangement*

This rearrangement, which degrades an acid into its next lower homologue, has been reviewed several times, first in 1934 by Franklin[836], then by Heldt and Donaruma[837] in 1960, and finally by Smith[838] in 1963.

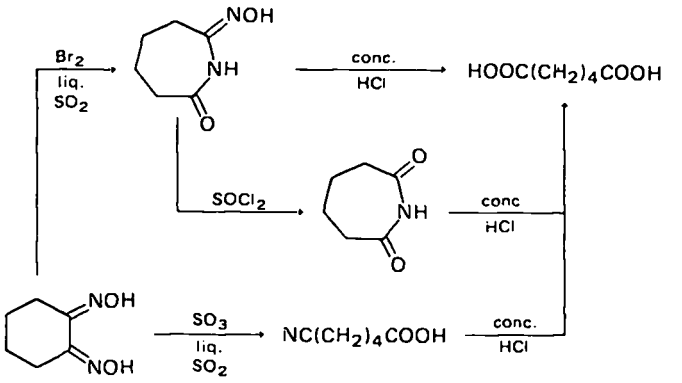
Although the most common Beckmann rearrangement involves treatment of an oxime with either concentrated sulphuric acid, phosphorus pentachloride and ether, hydrochloric acid–acetic acid–acetic anhydride mixtures or polyphosphoric acid[839] to produce a substituted amide, hydrolysis of the amide easily converts it into a carboxylic acid. Only those rearrangements which have been used to produce acids will be covered in this section.

A classic example of the use of the Beckmann rearrangement to prepare a carboxylic acid is that of Eck and Marvel[840] who treated cyclohexanone oxime with sulphuric acid to produce ε-caprolactam, which was then hydrolysed to ε-aminocaproic acid (equation 314).



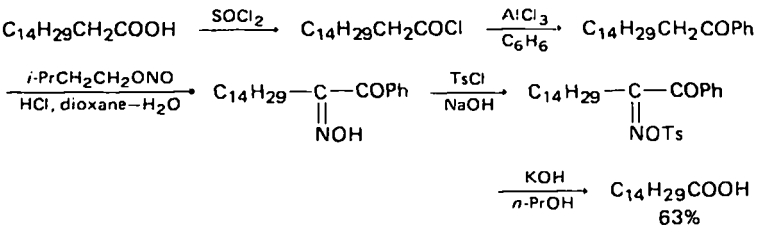
(314)

A similar approach was used[841] in the Beckmann rearrangement of 1,2-cyclohexanedione dioxime in liquid sulphur dioxide to produce adipic acid (equation 315).



(315)

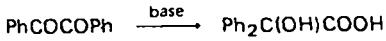
Dauben and coworkers[842] utilized the Beckmann rearrangement of an oxime tosylate to produce pentadecanoic acid from hexadecanoic acid via the intermediate formation of phenylpentadecyl ketone (equation 316).



(316)

3. *Benzilic acid rearrangement*

This rearrangement which has been most recently reviewed[843] in 1960, and which has been used essentially for the preparation of benzilic acid, involves the reaction of α-diketones with base causing rearrangement to the salts of α-hydroxy acids. For the preparation of benzilic acid itself from benzil (equation 317) a wide



(317)

variety of bases have been used, including concentrated aqueous potassium hydroxide[844], concentrated aqueous potassium hydroxide containing silver oxide[845], ethereal potassium hydroxide[846,847], and sodium amide in toluene[848]. The use of *o*-tolyllithium[849-851] and alkoxide ion has also been reported, and in the case of the alkoxide ion the benzilate ester is produced directly. With potassium *t*-butoxide–*t*-butyl alcohol in benzene the yield of *t*-butyl benzilate obtained (equation 318)[852] was 93%; however, with sodium methoxide the yield of methyl benzilate was considerably less[852]. Application of this rearrangement to aliphatic[853] and alicyclic[854] diketones as well as to substituted benzils[855,856] has also been reported.

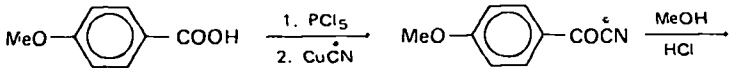
This rearrangement can also be applied to benzoin[857], which upon treatment with sodium bromate is first oxidized to benzil then converted to benzilic acid in

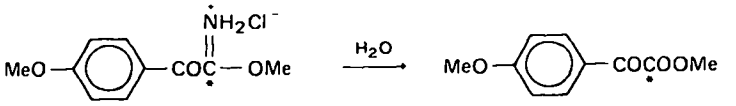
$$PhCOCOPh + K^+t\text{-}BuO^- \xrightarrow[C_6H_6]{t\text{-}BuOH} Ph_2C(OH)COOBu\text{-}t \qquad (318)$$

84–90% yield (equation 319), and to substituted benzoins such as α-*o*-tolylbenzoin[849-851].

$$PhCH(OH)COPh + NaBrO_3 + NaOH \xrightarrow[H^+]{H_2O} Ph_2C(OH)COOH \qquad (319)$$

Recently, Eastham[858] has reported that the benzilic ester rearrangement is irreversible. This rearrangement, which is the reverse of the benzilic acid rearrangement, begins with an ester, which upon treatment with base was thought to convert the ester into a benzil. For his study of this rearrangement, Eastham[858] used as his model methyl anisilate-1-^{14}C, which he prepared in 22% yield from anisic acid via





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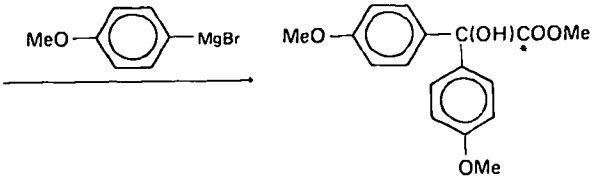

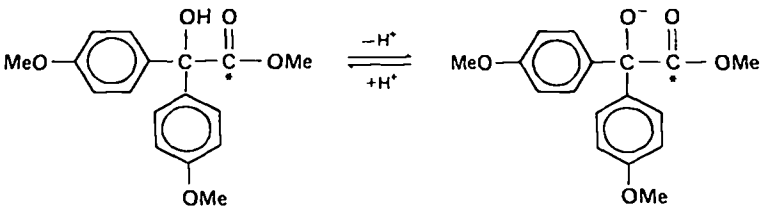

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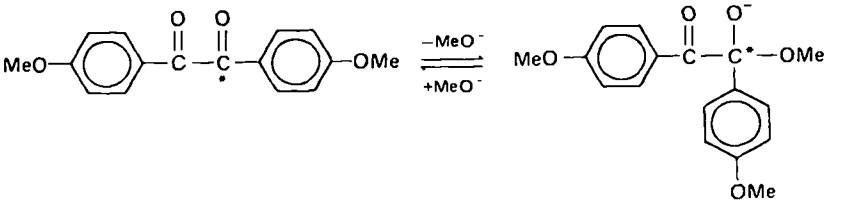


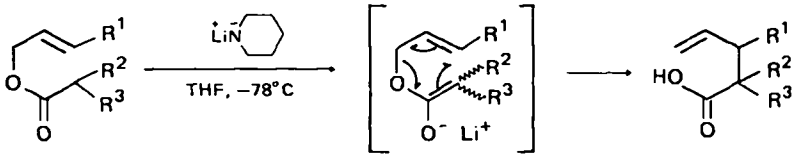
anisoyl cyanide-1-^{14}C, 4-methoxyphenylgloxylimino methyl ether-1-^{14}C hydrochloride and methyl-4-methoxyphenylglyoxylate-1-^{14}C (equation 320). This synthesis is novel because it is the first example of an imino ether hydrochloride being obtained from an aroyl cyanide.

The rearrangement Eastham proposed to study is shown in equation (321), using the methyl anisilate-1-^{14}C prepared above. In the scheme shown, k_2 is the step required for the benzilic acid rearrangement, while k_1 is the step under investigation. Treatment of methyl anisilate-1-^{14}C with potassium hydroxide followed by degradative saponification and oxidation with chromium trioxide, afforded only unlabelled dimethoxybenzophenone, a clear indication that no rearrangement had occurred.

4. Claisen rearrangement

This rearrangement which converts allyl aryl ethers, upon heating, to *o*-allylphenols has been reviewed by Tarbell[859] and Rhoads[860]. Although it is not common for the preparation of acids and/or esters, several reports have been made where acid or ester functions are present in the molecule during rearrangement, or where products from this rearrangement are converted into acids or esters, and our review of this rearrangement will be limited to such reports.

A typical example of the use of the Claisen rearrangement for the preparation of acids, which are then esterified using diazomethane, is the preparation of γ,δ-unsaturated acids from allyl esters (equation 322)[861]. In this study it was found that



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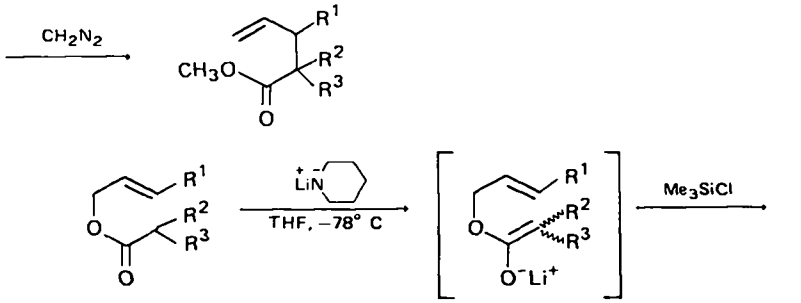
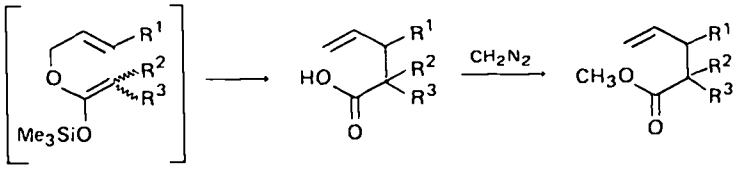


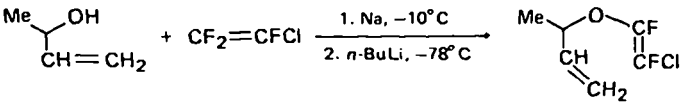
(323)



the allyl esters of tertiary and secondary acids rearranged rapidly at about room temperature as their lithium enolates, but that the acetates required quenching of these lithium enolates at −78°C with trimethylsilyl chloride before warming to effect good yields of rearranged acids (equation 323).

A similar Claisen rearrangement of trihalogenated analogues of allyl esters was reported by Normant and coworkers[862], who prepared the required difluorochlorovinyl allyl ethers by reaction of the sodium enolate of various 1-ene-2-ols with trifluorochloroethene. These products all rearranged at −35 to +25°C to afford γ,δ-unsaturated acid fluorides which were converted into the corresponding acids or esters by treatment with water or methanol, respectively (equations 324–328). The products can be rationalized on the basis of a [3,3]-sigmatropic Claisen-type rearrangement (equation 329).

A study of the stereoselectivity of the Claisen rearrangement of allyl siloxyvinyl ethers for the preparation of the Queen Butterfly pheromone has been recently reported by Katzenellenbogen and Christy[863]. Treatment of 2-bromopropene with



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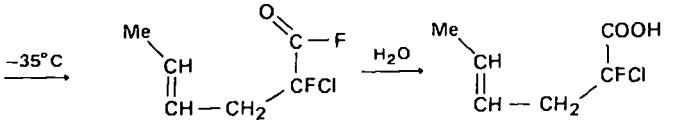

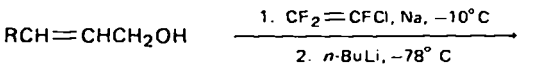

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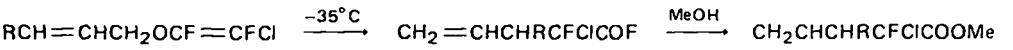
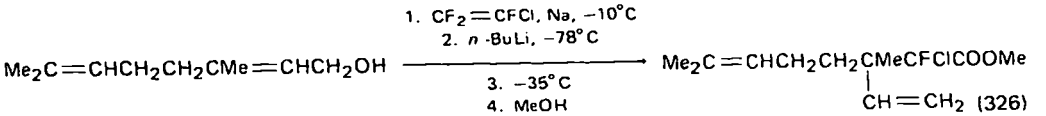
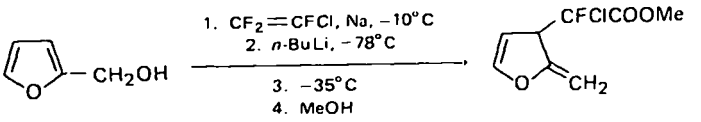




(326)



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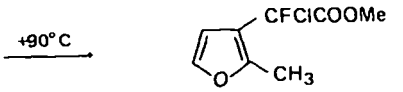
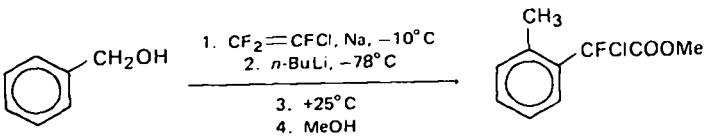
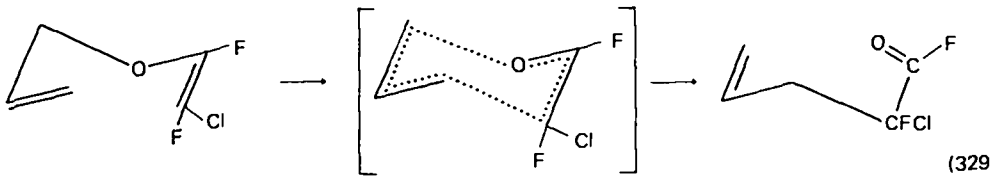




(328)



(329)

magnesium, followed by reaction of the resulting Grignard reagent with heptanal, afforded a 72% yield of 3-hydroxy-2-methyl-1-nonene which was converted into 3-acetoxy-2-methyl-1-nonene upon treatment with acetic anhydride in pyridine (equation 330). Derivatization of this product with isopropylcyclohexyl amine,

$$CH_3CBr{=}CH_2 \xrightarrow[\substack{I_2,\ N_2\\ 2.\ \text{heptanal}}]{1.\ Mg,\ THF,} n\text{-}C_6H_{13}CH(OH)CMe{=}CH_2 \quad (72\%)$$

$$\xrightarrow[\substack{\text{pyridine}\\ 40\ h,\ 25^\circ C}]{Ac_2O} n\text{-}C_6H_{13}CH(OAc)CMe{=}CH_2 \quad (92\%) \qquad (330)$$

n-butyllithium and trimethylsilyl chloride, afforded the corresponding trimethylsiloxyvinyl ether, which underwent the Claisen-type [3,3]-sigmatropic rearrangement in 53% yield and with a greater than 98% stereoselectivity, to give (*E*)-4-methyl-4-undecenoic acid, which was converted into its methyl ester by treatment with diazomethane (equation 331). Rearrangement of the *t*-butyldi-

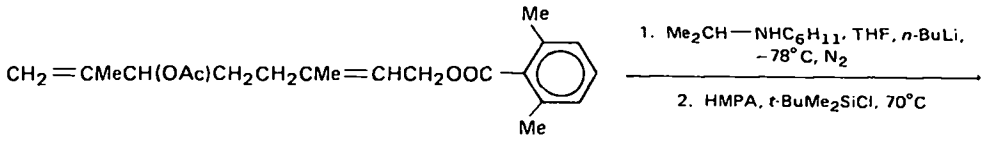
$$n\text{-}C_6H_{13}CH(OAc)CMe{=}CH_2 \xrightarrow[\substack{-78^\circ C,\ N_2\\ 2.\ Me_3SiCl,\ 70^\circ C}]{1.\ Me_2CH{-}NHC_6H_{11},\ THF,\ n\text{-}BuLi,}$$

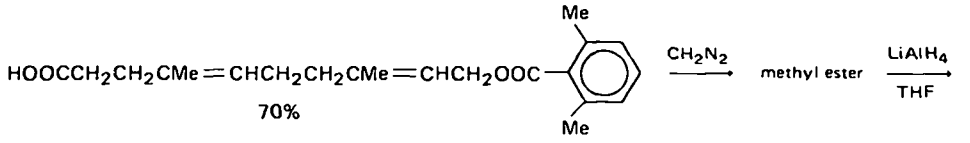
$$n\text{-}C_6H_{13}CH{=}CMeCH_2CH_2COOH \xrightarrow{CH_2N_2} n\text{-}C_6H_{13}CH{=}CMeCH_2CH_2COOMe \qquad (331)$$

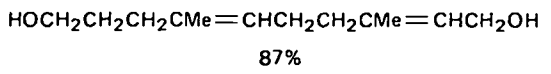
methylsiloxyvinyl ether derivative, prepared by treatment of 3-acetoxy-2-methyl-1-nonene with isopropylcyclohexyl amine, *n*-butyllithium and *t*-butyldimethylsilyl chloride, also afforded (*E*)-4-methyl-4-undecenoic acid in 80% yield, also with a very high degree of stereoselectivity. Application of this rearrangement to (*E*)-3-acetoxy-8-mesitoyloxy-2,6-dimethyl-1,6-octadiene prepared via a four-step synthesis from geraniol, afforded 70% of (*E*,*E*)-10-mesitoyloxy-4,8-dimethyl-4,8-decadienoic acid which, upon reduction and cleavage of the mesitoate, produced the pheromone (*E*,*E*)-3,7-dimethyl-2,6-decadiene-1,10-diol in 87% yield (equation 332). The intermediate acid was also converted into its methyl ester upon treatment with diazomethane.

The mechanism of this rearrangement (equation 333) again involves initial formation of the lithium enolate, which first undergoes *O*-silylation to afford the enol silyl ether and then undergoes the Claisen rearrangement.

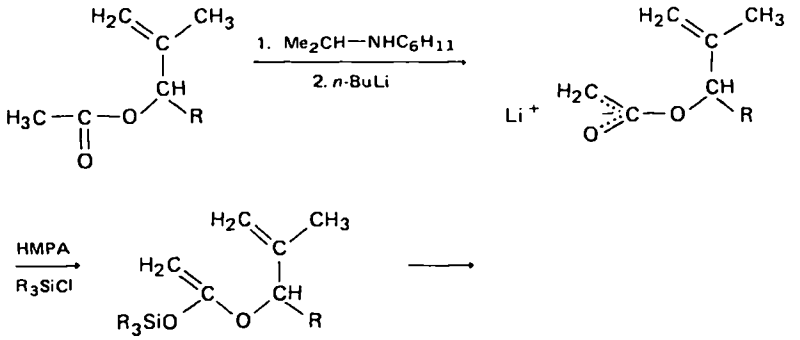
Upon treatment of monoacylated 4-methylcyclohex-3-ene-1,2-diol with two moles of 1-methoxy-1-dimethylamino ethylene, Lythgoe and coworkers[864] observed two successive alkoxy exchanges followed by a modified Claisen-type rearrangement, where the shift of a double bond caused concomitant stereospecific transfer of two $-CH_2CONMe_2$ groups to the former allyl termini, affording, after hydrolysis of the amide group, 1-methylcyclohex-3-ene-1,2-diacetic acid in 44%



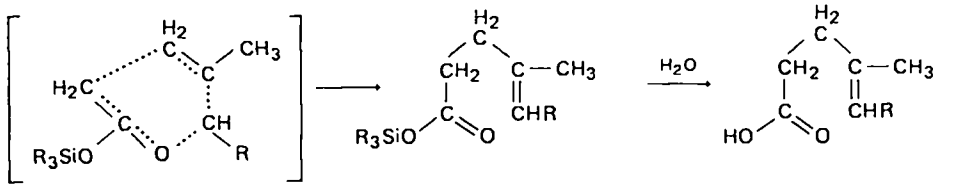




(332)

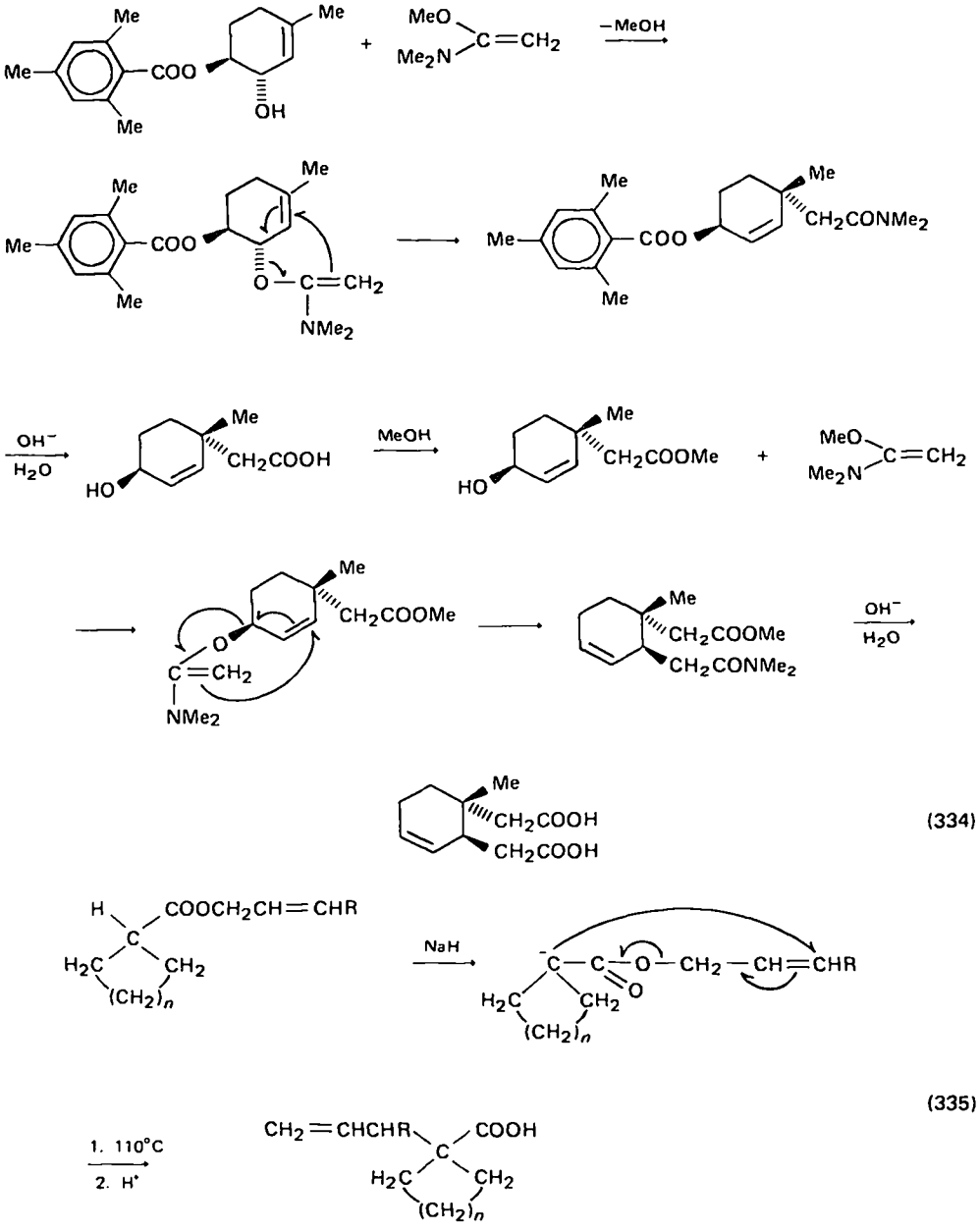


(333)



overall yield (equation 334). Additional examples of such rearrangements may be found in Section VII.C. This method, when applied to a mixed monoacetate, was shown[864] to be effective in allowing only the β,γ-unsaturated monoacetate to undergo two successive Claisen rearrangements, whereas the α,β-unsaturated monoacetate was recovered in the form of the diol after only one rearrangement (Scheme 6).

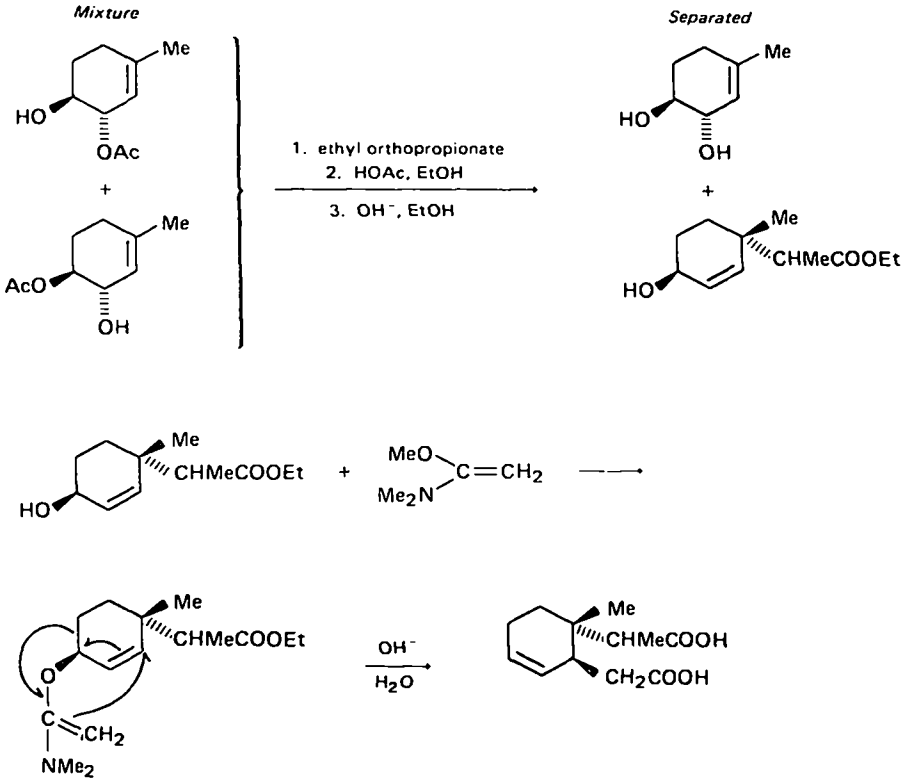
The ability of the anion derived from allylic esters of cycloalkanecarboxylic acids to undergo intramolecular allylation via a Claisen-type rearrangement has been shown by Arnold and Hoffman[865] to occur in about 40% yield. Allyl cyclopentane- and cyclohexanecarboxylates and cinnamyl cyclohexanecarboxylate were individually treated with sodium hydride to effect formation of the respective anions which upon heating at 110° for 24 hours, followed by acidification, afforded the corresponding acids (equation 335).



(334)

(335)

Abnormal Claisen rearrangements, that is, normal *ortho* Claisen rearrangement of a γ-alkylallylphenyl ether to an *o*-(α-alkylallyl)phenol followed by an isomerization of the side-chain of the phenol, have also been reported[866] in the literature. Since the mechanism of the secondary isomerization has been formulated as involving a cyclopropyldienone intermediate[866,867], Roberts and coworkers[868,869] reasoned that this mechanism should not be restricted to phenols,



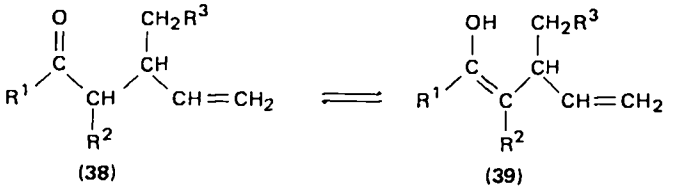
SCHEME 6.

but should be viewed as a general type of intramolecular rearrangement which could be utilized to convert one homoallylic carbonyl compound (38) to another (42) via the allylic enols 39 and 41 and the cyclopropyl carbonyl compound 40. These reports showed, not only that the sequence indicated in equation (336) occurs for a variety of substituted molecules, but also that it is reversible.

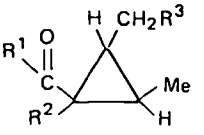
A new, synthetically useful, sigmatropic Reformatsky–Claisen rearrangement has also been reported[870], in which α-bromo esters derived from allylic and acetylenic alcohols are treated with zinc dust and undergo a [3,3]-sigmatropic rearrangement of the intermediate zinc enolate to afford γ,δ-unsaturated acids. Using this method α,α-dimethyl-α-allenic acid has been prepared in quantitative yields from 1-propynyl-3-(α-bromo-α-methylpropionate) (equation 337). The mechanism of this novel Claisen-type rearrangement is illustrated in equation (338) for the preparation of 2-methylhex-4-enoic acid from 1-butene-3-(α-bromopropionate).

5. *Favorskii rearrangement*

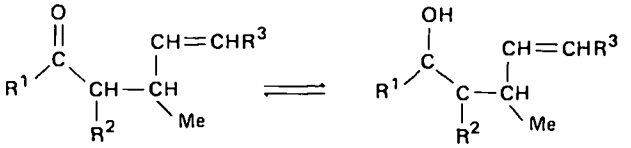
This rearrangement, which involves the reaction of α-chloro or bromo ketones with either alkoxide ion to produce rearranged esters, or with hydroxide ion to produce free acids (salts), has been reviewed at least three times by Jacquier[871] in 1950, by Tchoubar[872] in 1955, and, most recently, by Kende in 1960[873]. Although the normal Favorskii rearrangement involves the use of strong bases as



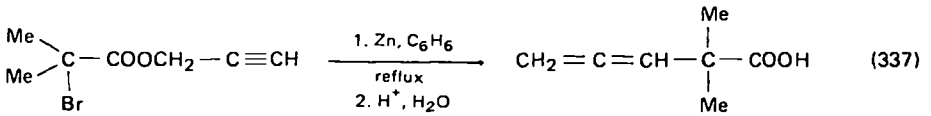
(38) (39)



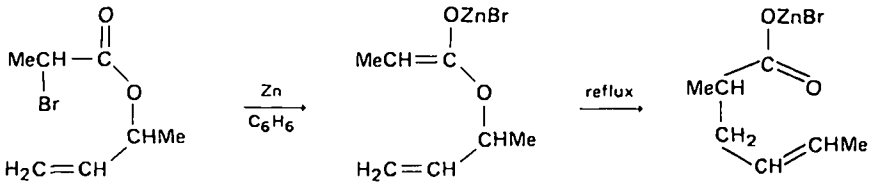
(40) (336)

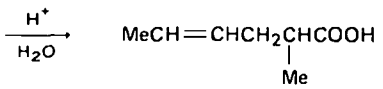


(42) (41)



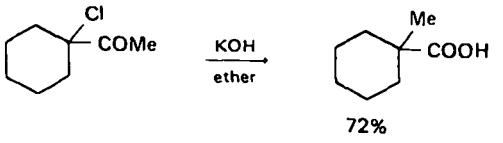
(337)



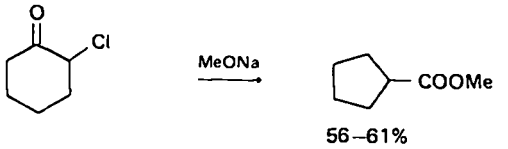


(338)

illustrated in equations (339)--(341) for the preparation of 1-methylcyclohexanecarboxylic acid[874], methyl cyclopentanecarboxylate[875] and long-chain fatty acids[876], mild bases have also been used. Sodium bicarbonate[877] has been used as the base in the preparation of *cis*-crotonic acid from 1,3-dibromo-2-butanone



(339)



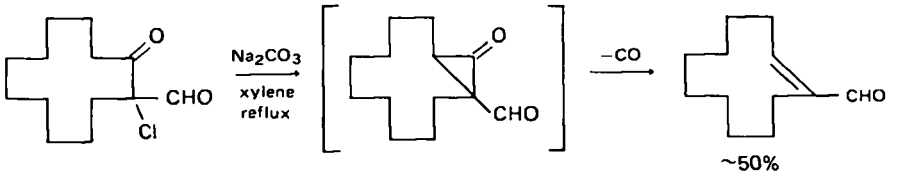
(340)

Straight chain acid chlorides + CH_2N_2 ⟶ Chloroketones $\xrightarrow{KOH}$ substituted fatty acids (341)

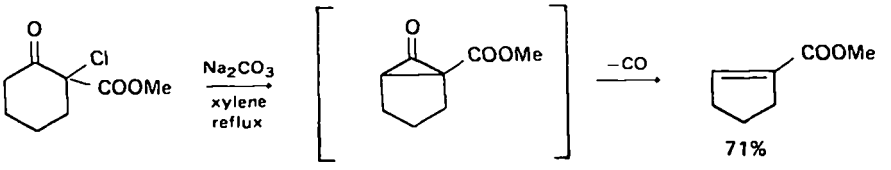
90%

(equation 342), while sodium carbonate in hot xylene has been used to prepare cyclopentenones in the synthesis of methyl jasmonate and jasmone[878], cyclopentenone intermediates for the synthesis of prostaglandins[879,880], cycloundecene-1-carboxaldehyde (equation 343)[881], and 1-carbomethoxycyclopentane from 2-chloro-2-carbomethoxycyclohexanone (equation 344)[881].

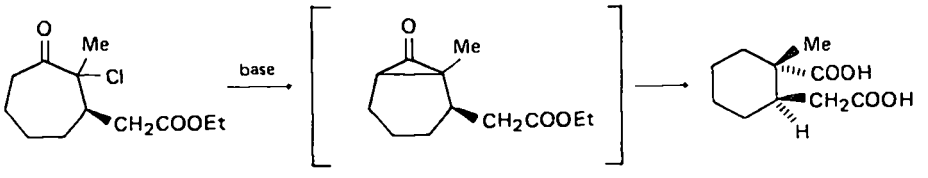
$$BrCH_2COCHBrMe + NaHCO_3 \xrightarrow[25°C]{H_2O} CH_3CH{=}CHCOOH \quad (342)$$



(343)



(344)

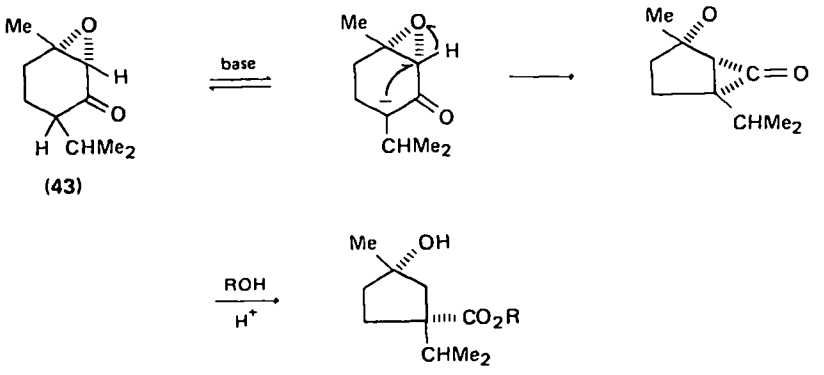


(345)

A study of the best conditions under which to run the Favorskii rearrangement, including the effect of the alkoxide types, their concentration and the resultant stereochemistry of the resulting products, has been made by Stork and Borowitz[882] for the preparation of *trans*-2-carboxycyclohexaneacetic acid (equation 345). Their findings showed the yield of product to decrease with the following order of alkoxide base used:

Benzyloxide ($C_6H_5CH_2O^-$) > ethoxide > methoxide > isopropoxide

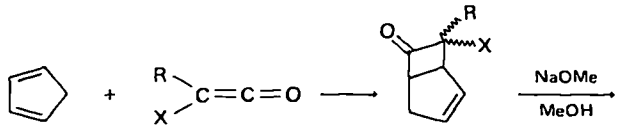
The non-stereospecificity of the Favorskii rearrangement in the reaction of piperitone oxide (43) and isophorone oxide with sodium methoxide or potassium hydroxide in methanol or methanol–water mixtures has also been reported (equation 346)[883].



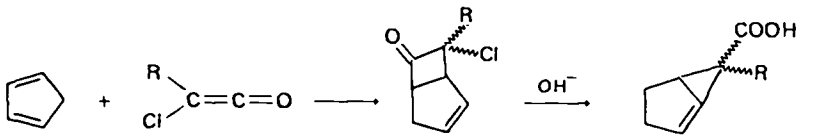
(43)

(346)

More recently, Favorskii-type rearrangements of haloketene olefin cycloadducts have appeared in the literature and a study of the stereospecificity of these rearrangements has also been reported. Thus, Brady and Hreble[884] have reported that rearrangement of a bicyclo[3.2.0]hept-2-en-6-one ring-system to the bicyclo-[3.1.0]hex-2-ene ring-system in the presence of sodium methoxide in refluxing methanol affords a product of unspecified stereochemistry (equation 347). In



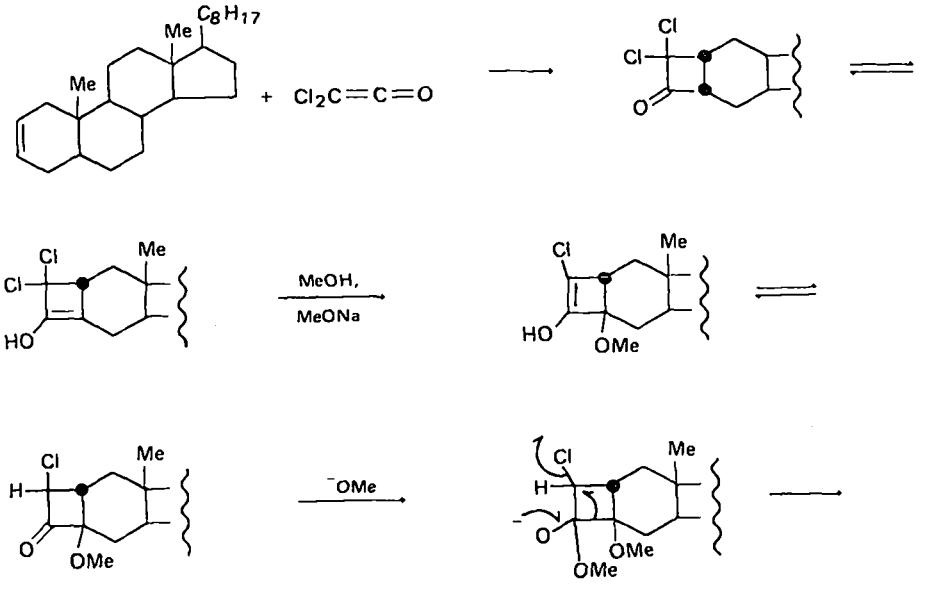
(347)

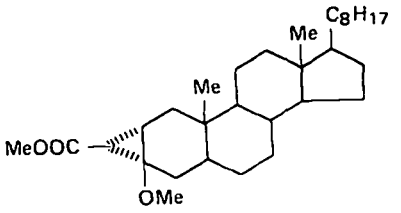


(348)

R = Me, Et, *i*-Pr
% = 97, 65, 0

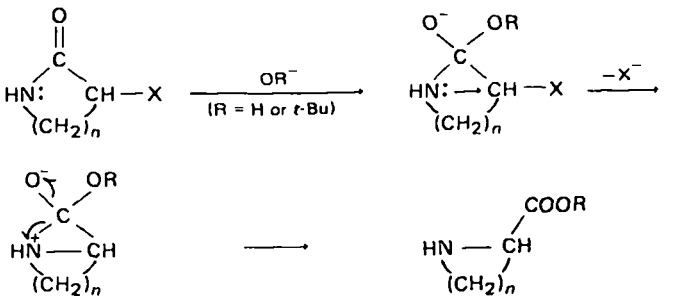
contrast, Harrison and coworkers[885,886] have reported a study of the same rearrangement using potassium hydroxide, which not only demonstrates that the *endo* acid is obtained from the *endo* haloketene olefin cycloadduct and the *exo* acid is obtained from the *exo* haloketene olefin cycloadduct, but that the proportion of *endo* haloketene olefin cycloadduct increases as the size of the alkyl group R on the ketene increases (equation 348). Fletcher and Hassner[887] has applied this rearrangement to the preparation of a 2 : 1 ratio of *endo* to *exo* bifunctional cyclopropane-containing steroids (equation 349).





(349)

endo: exo = 2:1

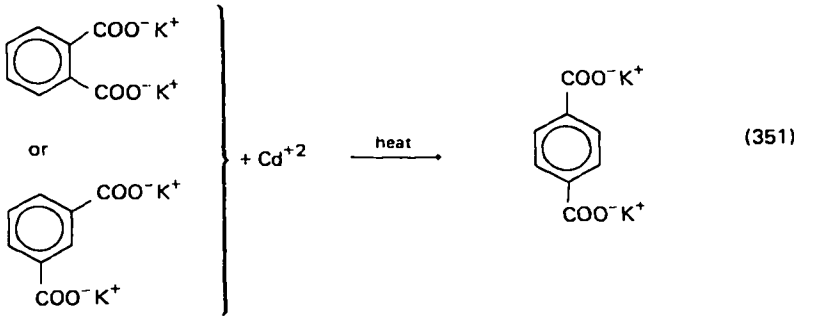


(350)

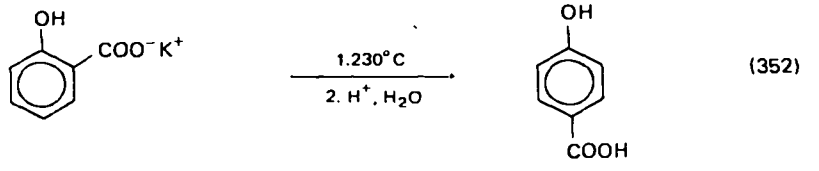
An extension of the Favorskii rearrangement to α-halogenated ω-amino lactams has also been reported[888]. In this case the initial lactam rearranges via a bicyclic aziridinone to an α-imino acid, affording a novel synthesis of medium ring-size cyclic α-imino acids homologous to proline. The reagent of choice for this rearrangement was found to be potassium *t*-butoxide in either *t*-butyl alcohol, tetrahydrofuran or dioxane, although sodium hydroxide in aqueous dioxane was also observed to afford product. The mechanism proposed is shown in equation (350).

6. Henkel reaction (Raecke process)

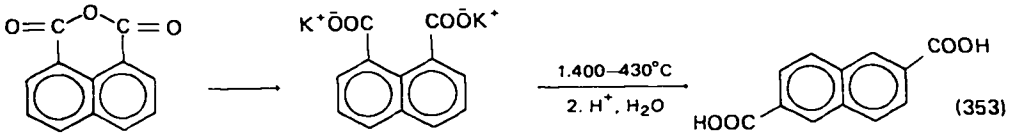
The Henkel reaction, which involves the thermal rearrangement or disproportionation of aromatic carboxylates of alkali metals to symmetrical aromatic dicarboxylates, has been reviewed[889]. This reaction is usually carried out between 200 and 500°C in an inert atmosphere and in the presence of catalytic quantities of cadmium salts, as exemplified[890] by the conversion of phthalic or isophthalic acid to terephthalic acid in 90–95% yield (equation 351), the rearrangement of salicylic acid to *p*-hydroxybenzoic acid in 70–80% yield (equation 352) and the conversion of 1,8-naphthalenedicarboxylic acid into 2,6-naphthalenedicarboxylic acid in 57–61% yield (equation 353)[891]. Similar results have been obtained[892] with 1- and 2-naphthoic acid, and naphthalene-1,3-, 2,3-, 1,6-, 1,8- and 2,7-dicarboxylic acids, all of which have been converted to 2,6-naphthalenedicarboxylic acid under a variety of conditions, using a variety of catalysts. The mechanism of this reaction has been studied by several investigators[892–895] and is believed to be intermolecular in nature.



(351)



(352)

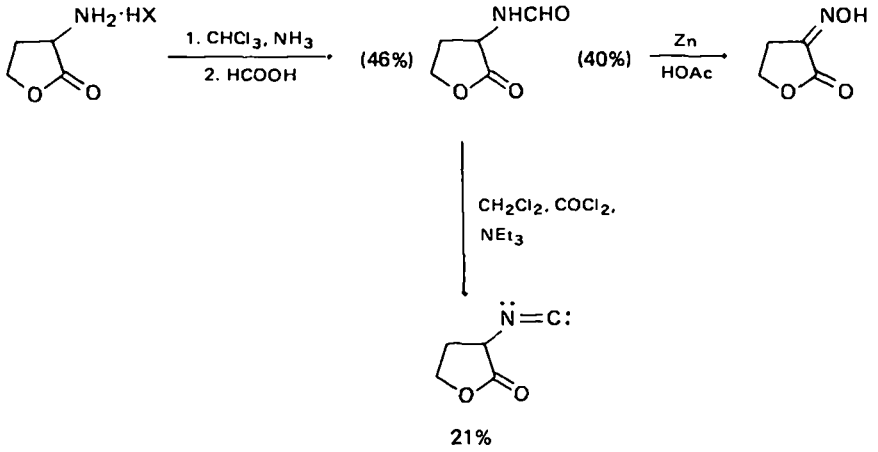


(353)

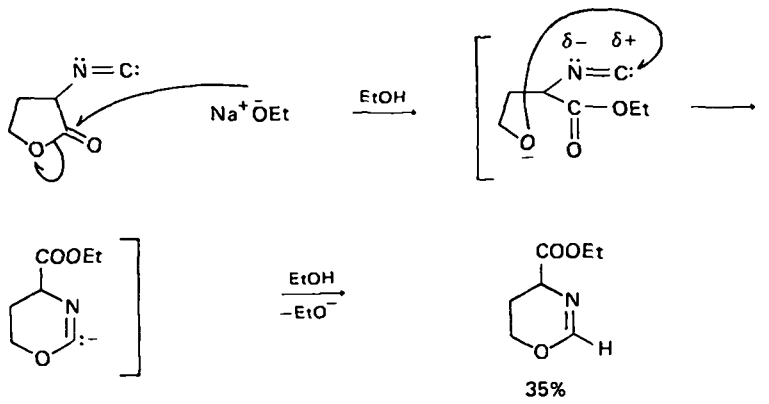
For additional information on this topic see the chapter on transcarboxylations by Ratuský in this volume.

7. *Isonitrile rearrangement*

Only one reference[896] appears in the current literature concerning the formation of an ester from an isonitrile, and this reaction involves the base-catalysed opening of the γ-lactone ring of α-isocyano-γ-butyrolactone to afford 35% yield of 4-carbethoxy-5,6-dihydro-4*H*-1,3-oxazine. The synthetic methods used for the preparation of α-isocyano-γ-butyrolactone and the mechanism of its base-catalysed ring-opening are shown in equations (354 and (355).



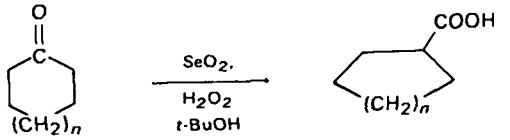
(354)



(355)

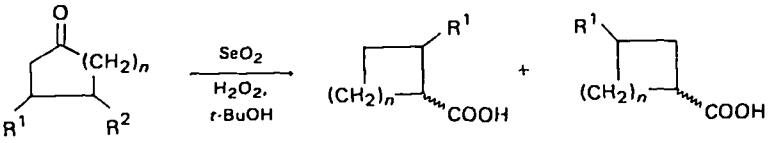
8. *Oxidative ring-contraction*

A variety of cyclic ketones have been treated with selenium dioxide–hydrogen peroxide mixtures to afford cyclic carboxylic acids containing one carbon less in the cycle (equation 356). These reactions all involve oxidative ring-contractions and



(356)

are not very effective since the yields are in the range of 20–40%[897,898] A study of alkyl-substituted cyclopentanone and cyclohexanone conversion to alkyl-substituted cyclobutanoic and cyclopentanoic acids has also been reported[899], in which the size of the alkyl group has been observed to affect the structure and stereochemistry of the resulting acids (equation 357). The mechanism for this rearrangement is not thoroughly understood.

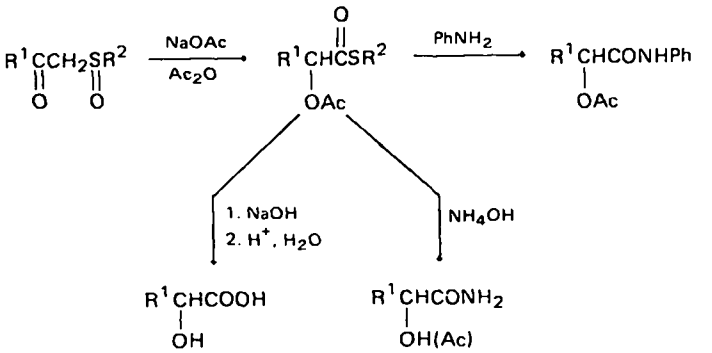


(44) (45) (357)

R¹	R²	n	Total yield (%)	44 (%)		45 (%)	
				cis	*trans*	*cis*	*trans*
Me	H	1	26	0	52	32	16
t-Bu	H	1	26	0	28	48	24
Me	H	2	25	11	25	36	28
H	Me	2	28	0	0	66	34
t-Bu	H	2	37	0	0	100	0
H	*t*-Bu	2	40	0	0	100	0

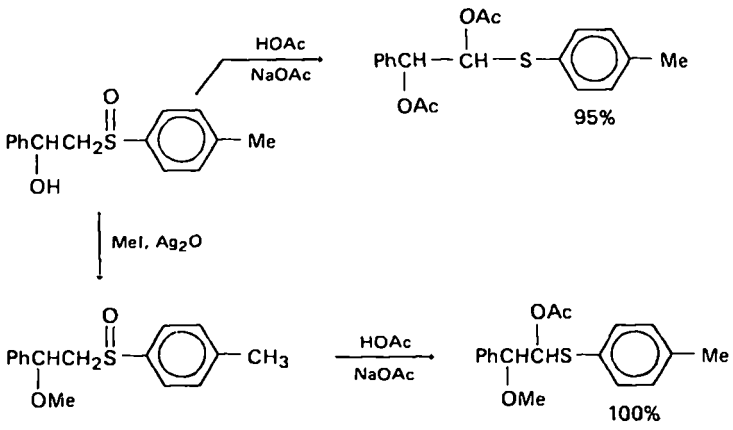
9. Pummerer rearrangement

This rearrangement is an intramolecular oxidation–reduction of sulphoxides, which upon treatment with acetate ion afford sulphides, with concomitant oxidation of the α-carbon. When applied to β-keto sulphoxides[900] this rearrangement affords α-acetoxy acid thio esters which can be hydrolysed to β-hydroxy acids, amides or substituted amides, depending upon which base is used for the hydrolysis (equation 358). When applied[901] to β-hydroxy sulphoxides such as 2-hydroxy-



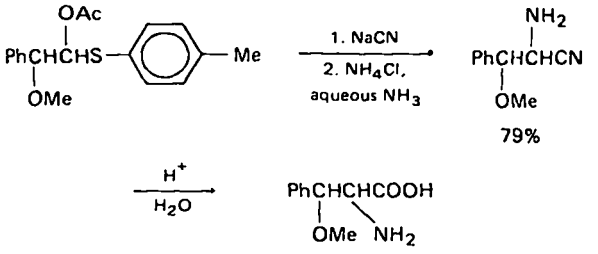
(358)

2-phenylethyl *p*-tolyl sulphoxide, a 95% yield of 1,2-diacetoxy-2-phenylethyl *p*-tolyl sulphide was obtained; however, if the β-hydroxy group is first methylated using methyl iodide and silver oxide, then the resultant 2-methoxy-2-phenylethyl *p*-tolyl sulphide is converted, in quantitative yield, to 1-acetoxy-2-methoxy-2-phenylethyl *p*-tolyl sulphide (equation 359). This product can be converted to



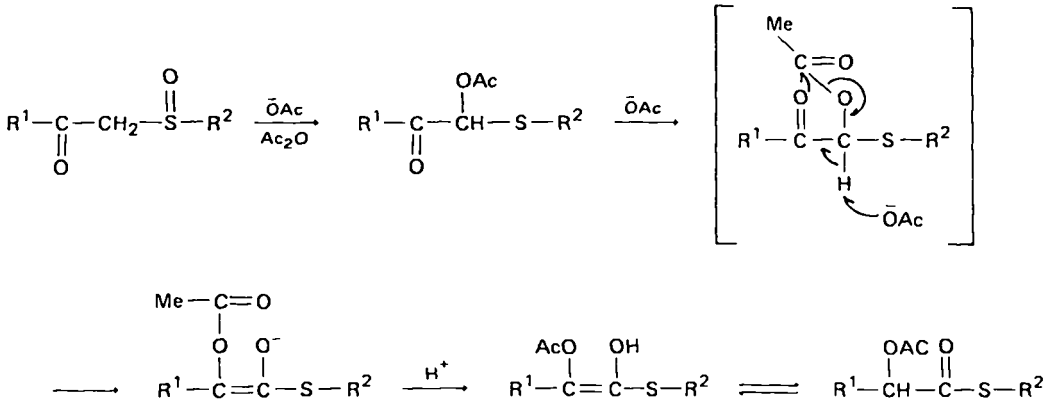
(359)

DL-*threo*-*O*-methylphenylserine in 57% yield via treatment with sodium cyanide, giving 2-amino-3-methoxy-3-phenylpropionitrile, followed by acid hydrolysis.



(360)

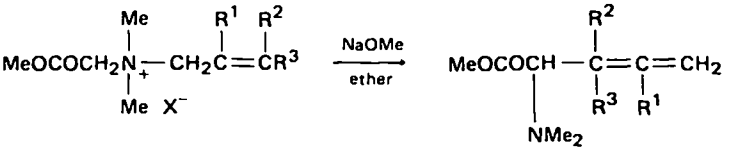
The mechanism[900] of this rearrangement is shown in equation (361) and is believed to involve initial formation of the α-acetate with reduction of the sulphoxide group followed by a base-catalysed intramolecular oxidation–reduction with concomitant acetyl transfer.



(361)

10. Stevens rearrangement

Two discussions of the Stevens rearrangement have appeared in the literature, the first by Zimmerman in 1963[902], and the second by Cram in 1965[903]. This rearrangement, which involves treatment of a quaternary ammonium salt containing an electron-withdrawing group on one of the carbons attached to the nitrogen with a strong base to produce a rearranged tertiary amine, has been used only once in the recent literature[904] for the preparation of amino substituted acids or esters. With the electron-withdrawing group attached to nitrogen being a carbalkoxymethyl group, substituted allyldimethyl ammonium halides upon treatment with sodium methoxide afforded 70–90% yield of γ,δ-unsaturated-α-dimethylamino-substituted esters (equation 362). Propargyl-substituted ammonium halides give rise to allenic esters (equation 363).



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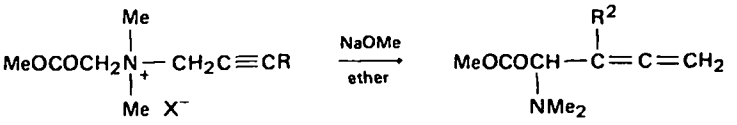
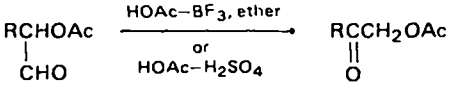


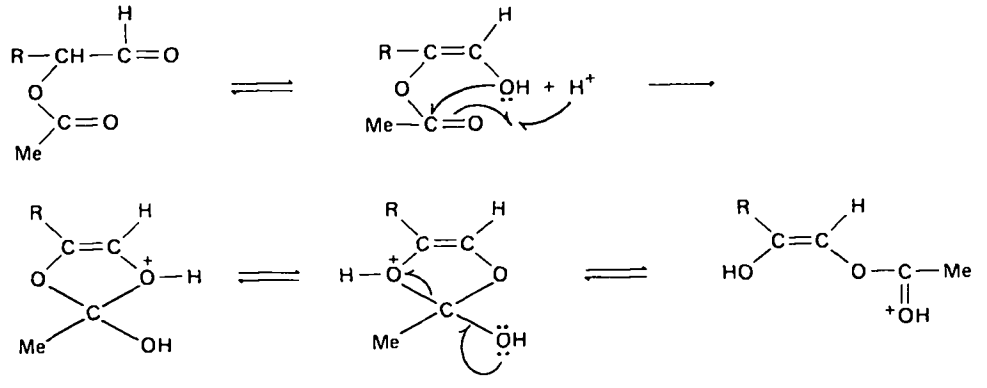
(363)

11. Miscellaneous rearrangements

A variety of miscellaneous rearrangements, which do not lend themselves to inclusion with the name rearrangements discussed above, but which lead to the



(364)



(365)

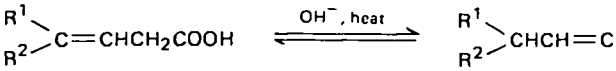
production of acids or esters, have also been reported in the literature. This section will attempt to discuss these rearrangements under the category of the catalyst which is used to effect the rearrangement.

a. Acid-catalysed rearrangements. Treatment of a variety of α-acetoxyl aldehydes with acetic acid–sulphuric acid mixtures or with acetic acid–boron trifluoride etherate mixtures has been reported[905] to produce > 90% yields of α-acetoxy ketones (equation 364). The isomeric ketones can be visualized as arising via the mechanism shown in equation (365).

A considerably more involved mechanism (Scheme 7) has been proposed[906] for the rearrangement of tricyclic ketones, such as 1,5-dimethyl-6-methylenetricyclo [3.2.1.$0^{2,7}$]oct-3-en-8-one, in neat formic acid (99%), at room temperature upon standing for 8–72 hours without exclusion of air, to the previously unreported ring-polymethylated phenylacetic acids. The yields range from 96% for the parent compound ($R^1 = R^2 = R^3 = R^4 = H$) to 25% for the methylated case ($R^1 = R^2 = R^4 = H$, $R^3 = Me$).

b. Alkoxycarbonyl group rearrangement. Although this type of rearrangement has been observed in reactions already discussed, such as the benzilic acid and the Favorskii rearrangements, other examples have also been reported in Michael additions, sigmatropic rearrangements and solvolytic reactions, all of which lead to acids or esters. An excellent review on the migrations of alkoxycarbonyl groups has been written by Acheson[907] and the reader is referred to this review for more detailed information.

c. Base-catalysed rearrangements. The base-catalysed rearrangements which lead to acids or esters are of two kinds, isomerization reactions and hydrolysis reactions. The base-catalysed isomerization reactions consist of the treatment of β,γ-unsaturated acids, esters or amides with a base such as potassium hydroxide and, in some cases, heat, to effect isomerization to the α,β-conjugated isomer. The pre-1943 work in this area has been reviewed by Gilman[908]. Two more recent examples of this type of isomerization reaction, which have appeared in the literature, consist of the base-catalysed isomerization of γ,γ-disubstituted-β,γ-unsaturated butanoic acids[909] to γ,γ-disubstituted-α,β-unsaturated butanoic acids (equation 366), and the isomerization of 1,4-dihydrobenzoic acid to 3,4-dihydrobenzoic acid in 80% yield (equation 367)[910].



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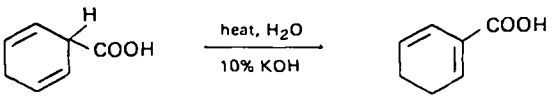
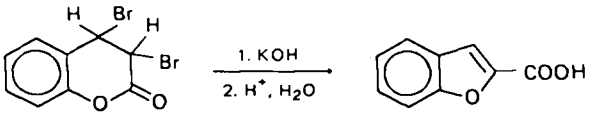
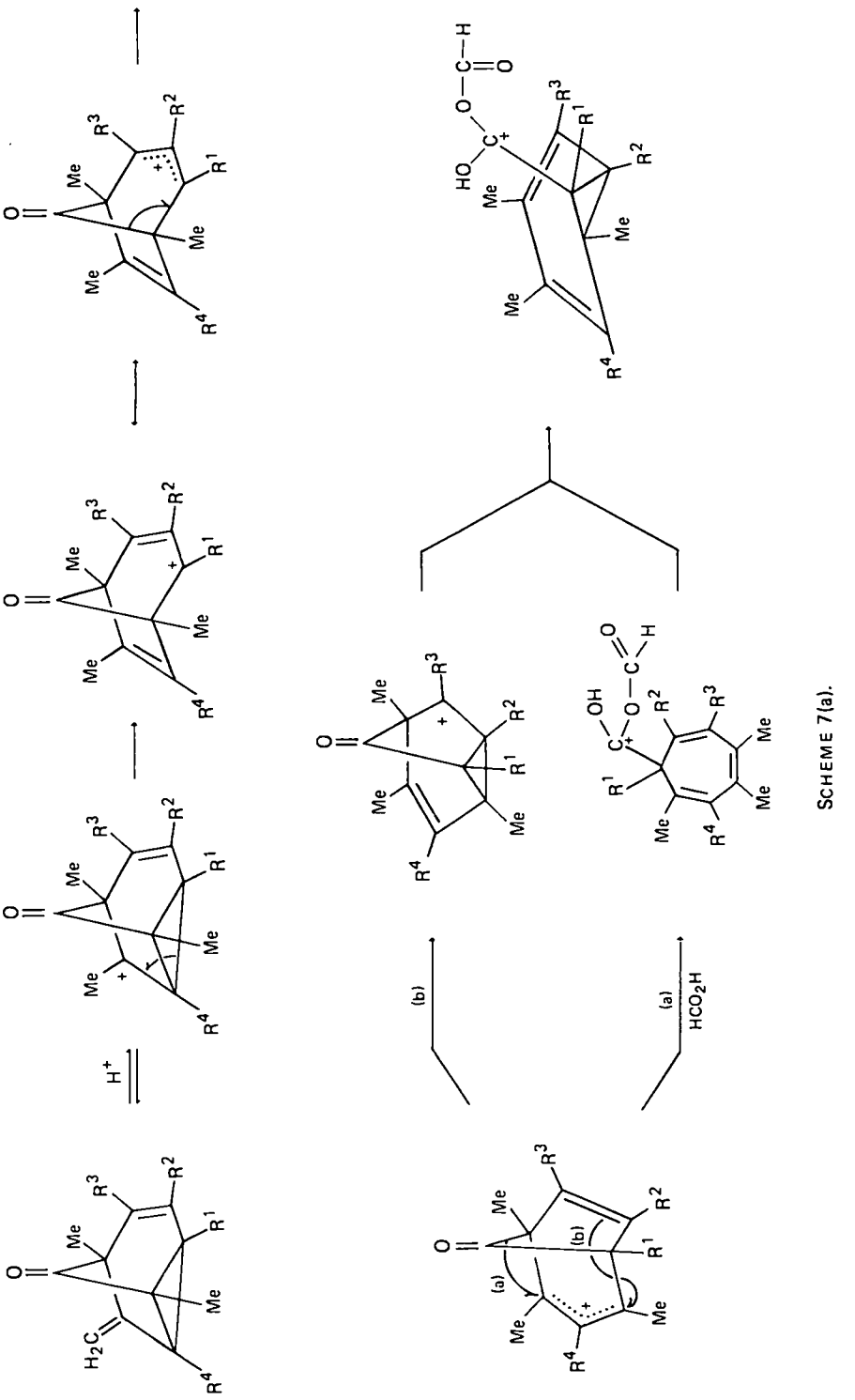


(367)

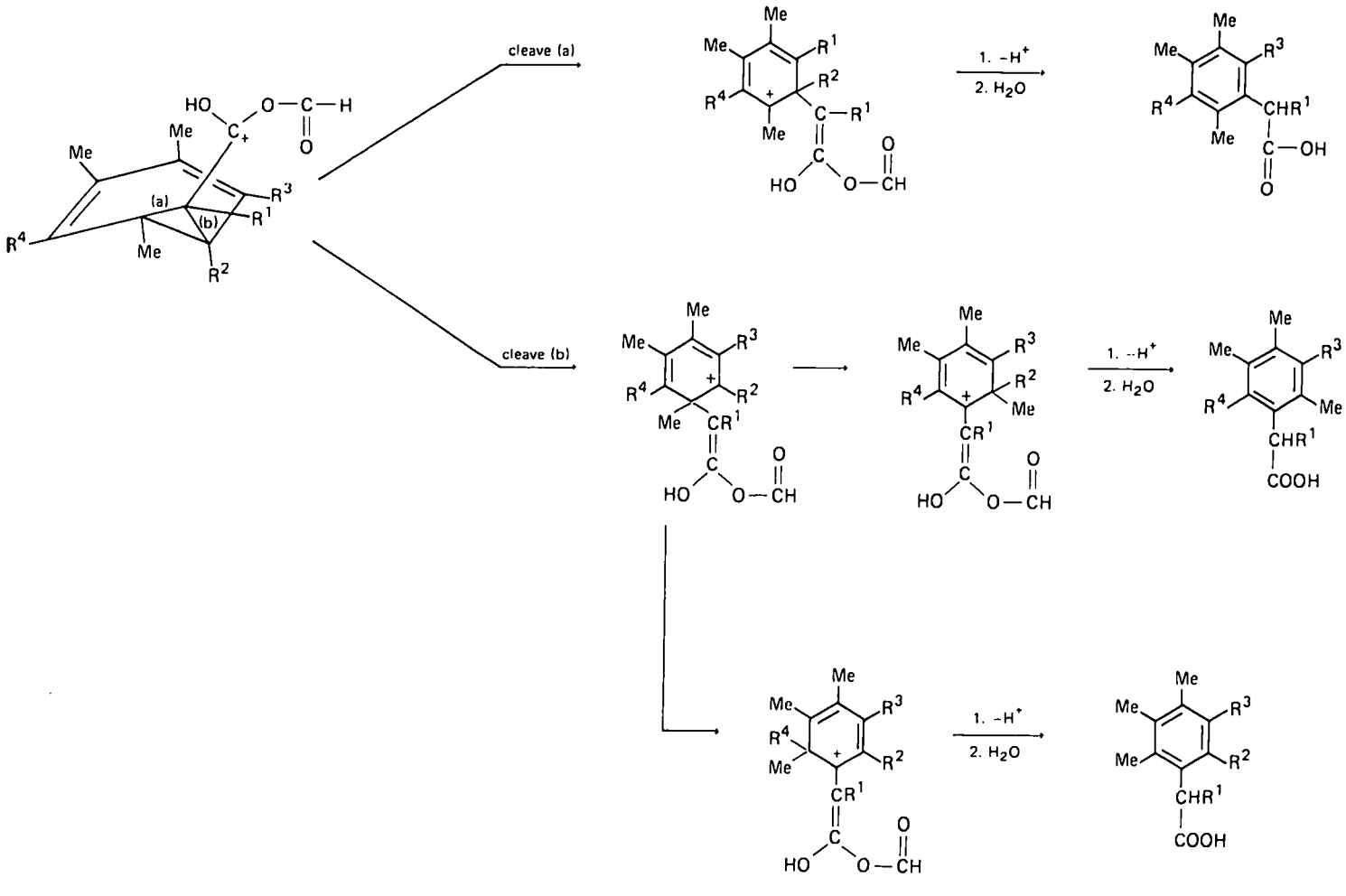
The base-catalysed hydrolysis reactions which lead to rearranged acids or esters have been applied to a variety of compounds. Coumarin dibromide has been converted to coumarilic acid in 82–88% yield upon treatment with potassium hydroxide followed by acidification (equation 368)[911]. Isatin has been converted



(368)

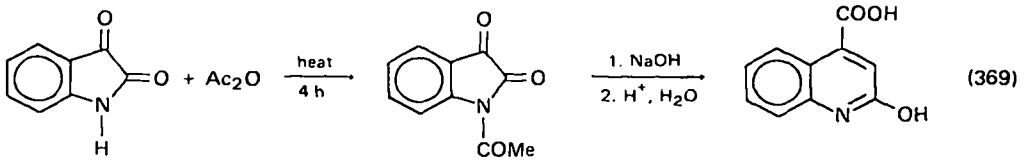


SCHEME 7(a).



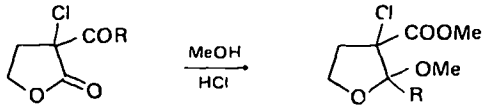
SCHEME 7(b).

to 2-hydroxycinchoninic acid in 70–73% yield via treatment of the intermediate *N*-acetylisatin with sodium hydroxide followed by acidification (equation 369)[912].



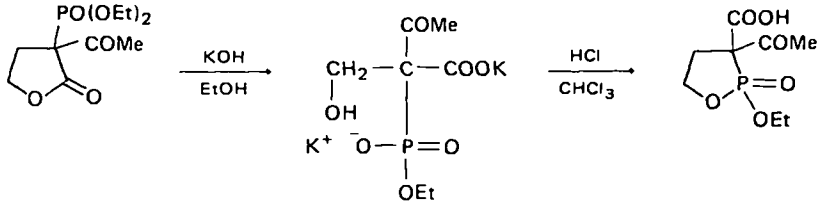
(369)

Base-catalysed hydrolysis of lactones has also led to rearranged acids as illustrated by the reports of Korte and coworkers. Based upon their initial findings that α-alkyl[913] and α-halogen-α-acyl lactones[914] upon treatment with hydrochloric acid in methanol afforded 2-methoxy-3-chloro-3-carbomethoxy tetrahydrofuran derivatives (equation 370), they then investigated the reaction of α-phosphonic acid



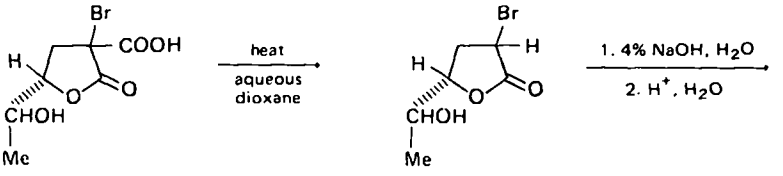
(370)

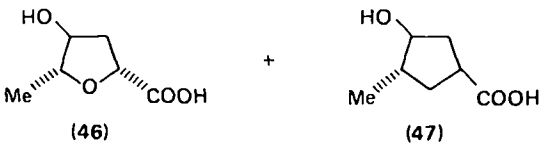
ester substituted α-acyl lactones. Korte found that treatment of the diethyl ester of α-acetyl-γ-butyrolactone-α-phosphonic acid with potassium hydroxide in ethanol followed by treatment with hydrochloric acid in chloroform afforded the ethyl ester of α-acetyl-α-carboxy-γ-phostone[915] via a ring-opened intermediate (equation 371).



(371)

A similar rearrangement of α-bromo-α-carboxy-γ-substituted γ-butyrolactone to a stereochemical mixture of 4-hydroxy-5-methyl-2-tetrahydrofuroic acid has been reported[916] upon decarboxylation of the lactone in aqueous dioxane, followed by hydrolysis of the intermediate bromolactone with 4% sodium hydroxide (equation 372). A stereospecific synthesis of the *cis* isomeric acid **46**, can also be accom-

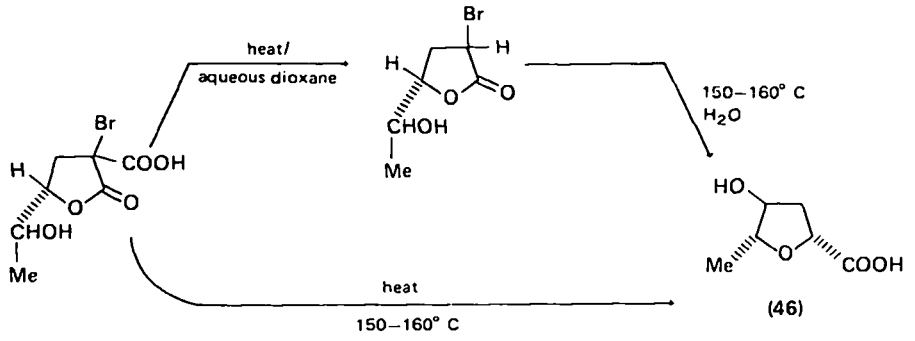




(372)

(46) (47)

plished by decarboxylation as above, followed by hydrolysis at 150–160°C in water, or, more directly, by decarboxylation of the starting lactone upon heating in a sealed tube at 150–160°C for one hour (equation 373). The mechanism for these rearrangements is shown in equation (374) assuming the *trans* configuration of the intermediate bromo lactone.



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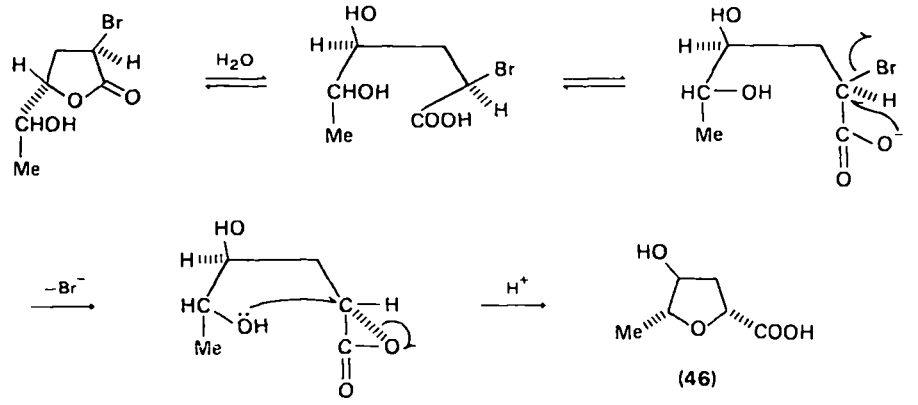

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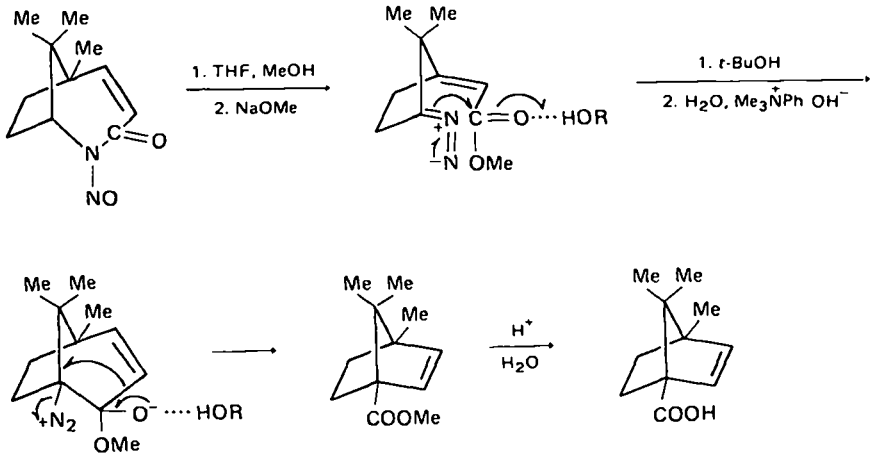
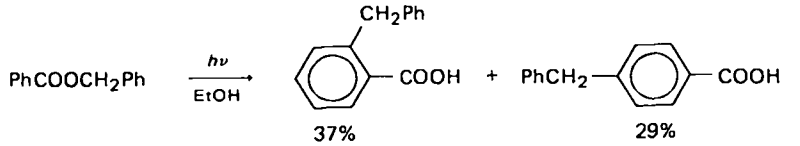


(375)

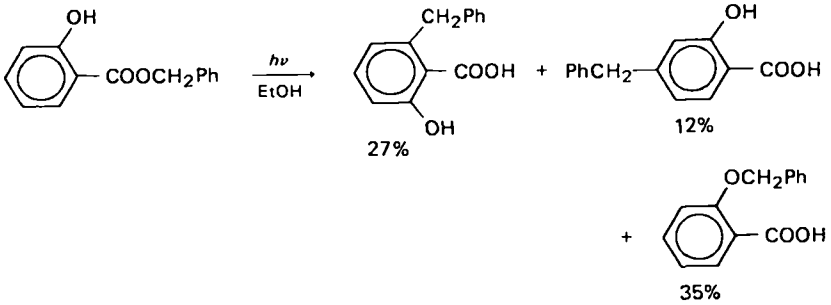
Base-catalysed rearrangements of bicyclic compounds have also been reported. Treatment[917] of 6,9,9-trimethyl-2-nitroso-2-azabicyclo[4.2.1]non-4-en-3-one with methanol in THF followed by reaction with sodium methoxide affords methyl *cis*-β-(3-diazo-1,2,2-trimethylcyclopentyl)acrylate, which upon reaction with *N,N,N*-trimethylanilinium hydroxide afforded a 90% yield of methyl 4,7,7-trimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate. Acidification of the ester afforded 89% of the corresponding acid (equation 375). Additional studies in this series have also been reported[918].

d. Photochemical rearrangements. Photochemically-induced rearrangements for the production of acids and esters have been applied to a variety of compounds. In most types of photochemical rearrangements the presence of a substituent on the starting material, rather than simply effecting the rate of the reaction, actually causes a different product to be formed. For example, room-temperature photolysis of an ethanol solution of benzyl benzoate[919] affords only *ortho*- and *para*-benzylbenzoic acids (equation 376). However, when an *ortho*-hydroxy substituent



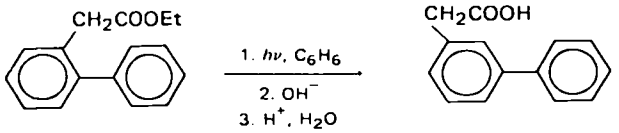
(376)

is present in the benzyl benzoate starting material, 2-benzyloxybenzoic acid is the major product formed upon photolysis (equation 377)[919].

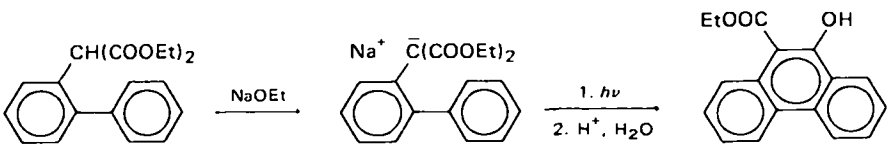


(377)

Similar results are obtained[920] upon photolysis of a benzene solution of *o*-biphenylyl acetate, which after hydrolysis and acidification affords *m*-biphenylylacetic acid (equation 378), while photolysis of the α-anion of diethyl *o*-biphenylylmalonate produces[920] ethyl 10-hydroxy-9-phenanthroate via intramolecular photoacylation of the intermediate enolate (equation 379). This type of photo-

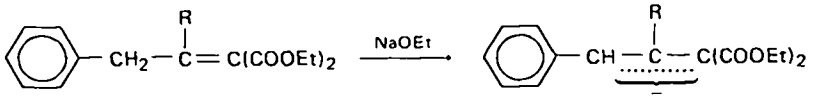


(378)



(379)

acylation was also observed[920] when the anion of phenylethylidenemalonic ester was photolytically ring-closed (equation 378). The mechanism used to explain these intramolecular photoacylation reactions (equations 381 and 382) requires that the non-bonding 2*p* electrons of the carbanion (or heteroatom Y) be delocalized onto the phenyl or biphenyl system in the electronically excited state producing an increase in the electron density at the *ortho* positions in the excited state of the enolate ion.



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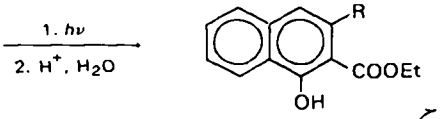

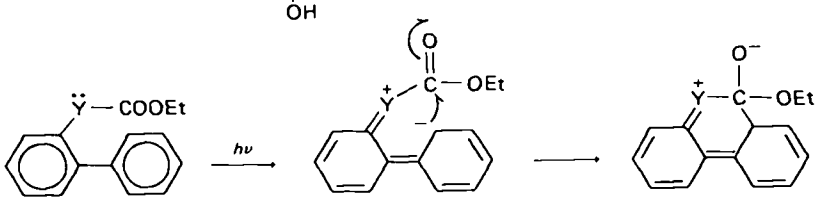

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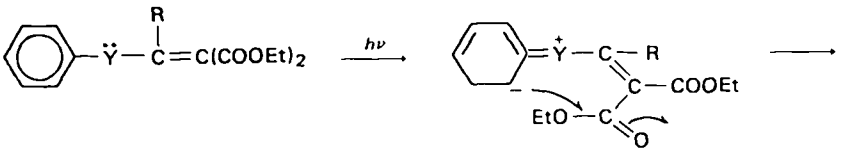
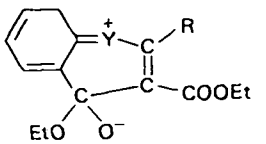
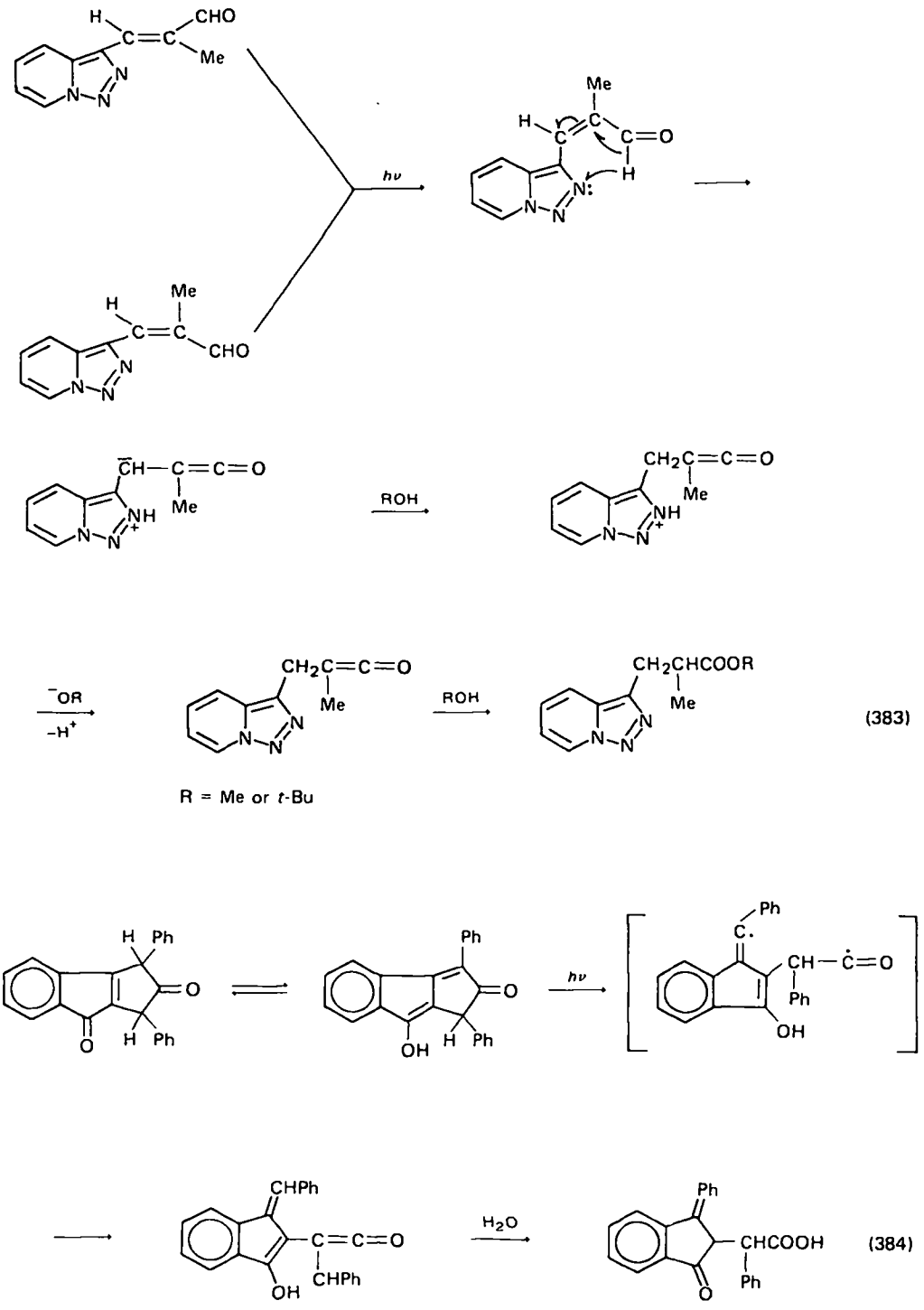




(382)

The presence of a lone electron pair has also been shown to be required in the photochemical conversion of *cis*- and *trans*-acraldehydes to methyl and *t*-butyl 3(3-*v*-triazolo[1,5-a]pyridyl-2-methylpropionate in 74 and 59% yields, respectively. The mechanism proposed for these conversions is shown in equation (383). A similar mechanism can be used to explain the conversion[921] of *v*-triazolylacraldehyde in 92% yield to methyl 3-(1-methyl-*v*-triazol-4-yl)propionate upon photolysis in methanol or in 29% yield to 3-(1-methyl-*v*-triazol-4-yl)propionic acid upon photolysis in water.

An interesting photochemically-induced ring-cleavage reaction[922] producing an acid has also been reported, in which 2,8-dioxo-1,3-diphenyl-1,2,3,8-tetrahydro-(cyclopenta-[a]-indene) has been converted in 39% yield to 1-oxo-2-(α-carboxy-benzyl)-3-benzylidene indane (equation 384).



R = Me or *t*-Bu

(383)

(384)

III. SYNTHESIS OF ESTERS

A. Esters by Solvolytic Reactions

Direct conversion of carboxylic acids and acid derivatives into esters by reactions with hydroxylic compounds are designated here as solvolysis reactions. Included are reactions of acids with alcohols, alcoholyses of acyl halides, anhydrides, ketenes, nitrites and amides, and transesterifications. Reactions of carboxylate salts with alkylating agents, although not strictly solvolytic processes, are also included.

1. Direct esterification of acids

The most frequently encountered method for preparation of esters from carboxylic acids involves reaction of the free acid with an alcohol in the presence of a mineral acid catalyst at reflux (equation 385). Such reactions are equilibrium

$$R^1COOH + R^2OH \overset{H^+}{\rightleftharpoons} R^1COOR^2 + H_2O \qquad (385)$$

processes, and must be displaced toward the desired ester by use of an excess of one of the reactants, usually the alcohol, or by removal of water. Primary and secondary alcohols usually react satisfactorily, whereas tertiary alcohols and phenols participate poorly because of competing elimination and poor nucleophilicity, respectively. As would be expected for reactions which involve nucleophilic addition of the hydroxy component to the protonated carboxyl group of the acid, sterically hindered acids are esterified with difficulty under these conditions[923].

Among the catalysts used for direct esterification, sulphuric acid alone[924-926] or in the presence of molecular sieves[927,928], hydrogen chloride[929,930] and arylsulphonic acids[931-933] are the most popular. Acidic ion-exchange resins in conjunction with a dehydrating agent such as calcium sulphate are also effective catalysts[933,934]. Polymer-protected aluminium chloride, a complex between anhydrous aluminium chloride and polystyrene–divinylbenzene copolymer, can serve as both a Lewis-acid catalyst and a dehydrating agent to effect esterification of alkyl and aryl acids with primary and secondary alcohols under mild conditions[935]. Along similar lines, graphite bisulphate, an intercalated complex, prepared by electrolysis of 98% sulphuric acid with a graphite anode, functions very effectively as a catalyst for esterification of various acids with primary and secondary alcohols[936].

A great deal of attention has been focused on the use of boron trifluoride as a catalyst for esterification. Several different procedures can be used with this reagent. For example, methyl esters can be prepared from various acids by refluxing with two molecular equivalents of the commercial boron trifluoride–methanol complex in excess methanol[937]. Alternatively, boron trifluoride–etherate can be used as a catalyst for preparative-scale esterification. In these reactions the alkyl group of the resulting ester is not limited to methyl, as in the preceding case. Boron trifluoride etherate–alcohol esterifications are usually carried out by refluxing the acid with 1–2 equivalents of catalyst and a 10–15 molar excess of the appropriate alcohol. This mild, effective method has been designated in a recent review[938] as perhaps the most generally satisfactory procedure for direct esterification of carboxylic acids.

Trifluoroacetic anhydride can be used to promote rapid esterification of acids with both alcohols and phenols[939-943]. The mixed anhydride formed by reaction

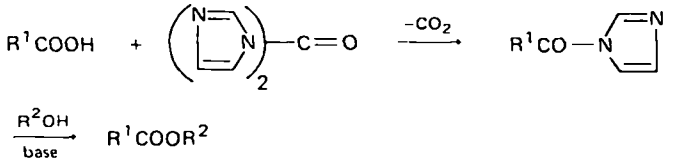
of trifluoroacetic anhydride with the carboxylic acid is apparently the reactive intermediate. A related process involves treatment of a mixture of an acid and alcohol in pyridine with an aromatic sulphonyl chloride (equation 386)[944,945].

$$R^1COOH \xrightarrow[\text{pyridine}]{ArSO_2Cl} (R^1CO)_2O \xrightarrow{R^2OH} R^1COOR^2 \qquad (386)$$

This reaction proceeds through *in situ* formation of the symmetrical anhydride, which then reacts with the hydroxylic compound. Aliphatic and aromatic acids can be used, and phenols as well as tertiary alcohols afford high yields of esters.

Several acid-catalysed esterification procedures are especially useful for the preparation of phenyl esters. One of the most versatile involves treatment of a carboxylic acid with a phenol in the presence of 1–5 mole % of a mixture of boric and sulphuric acids in toluene, xylene, or sulpholane–xylene[946]. Azeotropic removal of water gives the phenyl esters in high yield. Neither sulphuric acid nor boric acid alone catalyses the reaction. Polyphosphate esters, prepared by reacting diethyl ether with phosphoric oxide in chloroform, can be used to promote aryl ester formation[947]. Diphenyl phosphite in pyridine also serves to effect formation of phenyl esters from free acids and phenols[948,949]. Triphenylphosphine ditriflate, obtained *in situ* from triphenylphosphine and trifluoromethanesulphonic acid, has been shown to be an efficient electrophilic catalyst for esterification of free acids with both phenols and tertiary alcohols[950].

If acidic conditions are to be avoided, a number of efficient procedures are available. For instance, dicyclohexylcarbodimide (DCCD)[951,952] or β-trichloromethyl-β-propiolactone[953] can be used to effect esterification of carboxylic acids with alcohols and phenols. Reaction of carboxylic acids with equimolar amounts of an alcohol and *N,N'*-carbonyldimidazole constitutes a mild procedure for the synthesis of various esters (equation 387)[954]. The acid reacts initially with *N,N'*-carbonyldiimidazole to evolve carbon dioxide and form an *N*-acylimidazole (imidazolide). This intermediate then acylates the alcohol. The acylation step is catalysed by basic reagents such as sodium ethoxide, alkali metal amide or imidazolyl sodium. Hindered acids and tertiary alcohols participate readily in these reactions.

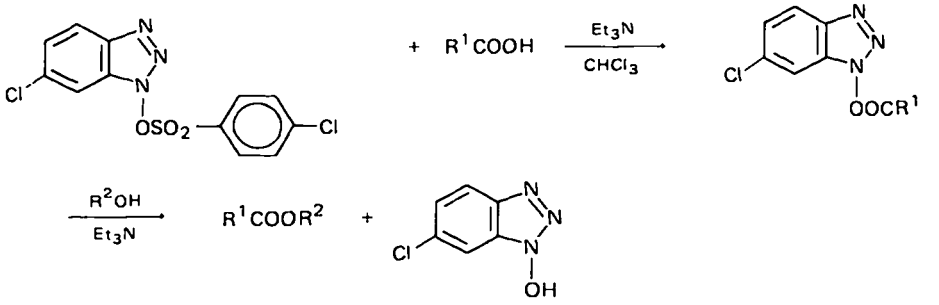


(387)

Esters can be prepared under neutral conditions at room temperature by the reaction of carboxylic acids with alcohols in presence of molar amounts of triphenylphosphine and diethyl azodicarboxylate (equation 388)[955]. Esterification of chiral alcohols by this procedure leads to inversion of configuration at the carbinol carbon[956].

$$R^1COOH + R^2OH \xrightarrow[Ph_3P,\ ether]{EtOOCN=NCOOEt} R^1COOR^2 + Ph_3PO + EtOOCNHNHCOOEt \qquad (388)$$

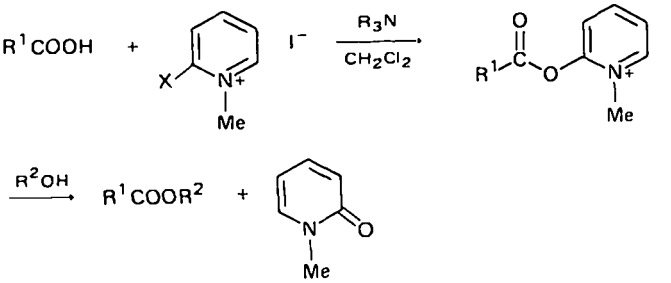
A mild esterification method for carboxylic acids employs sulphonate coupling reagents such as 6-chloro-1-*p*-chlorobenzensulphonyloxybenzotriazole (equation 389)[957]. This procedure consists of two steps, the first of which is condensation of



(389)

a carboxylic acid with the triazole to form an active carbamate-type ester. Alcoholysis of this intermediate with primary or secondary alcohols then affords the ester.

A new method for the preparation of esters, which is satisfactory for both hindered acids and tertiary alcohols, is based on the reaction of equimolar amounts of a carboxylic acid and an alcohol or phenol in the presence of 1.2 equivalents of 1-methyl-2-halopyridinium iodide and 2.4 equivalents of a tertiary amine (equation 390)[958]. The reaction proceeds by initial formation of a 2-acyloxypyridinium salt, which then reacts with the alcohol to produce the ester and *N*-methyl-2-pyridone.



(390)

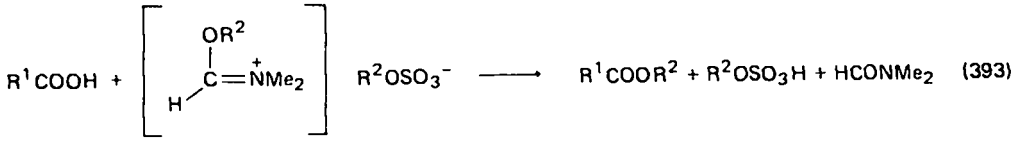
Reaction of carboxylic acids with diazoalkanes represents a widely used method for ester preparation (equation 391)[959-961]. However, the toxic and potentially explosive characteristics of these reagents renders them impractical for preparative-scale esterifications.

$$R^1COOH + R^2CHN_2 \longrightarrow R^1COCH_2R^2 + N_2 \qquad (391)$$

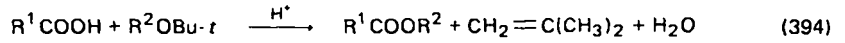
Several other esterification methods also utilize reagents other than alcohols as the source of the alkoxy function of the resulting esters. For instance, dialkyl acetals of *N*,*N*-dimethylformamide react with various acids to afford esters in good yields (equation 392)[962,963].

$$R^1COOH + H{-}C(OR^2)_2{-}NMe_2 \longrightarrow R^1COOR^2 + R^2OH + HCONMe_2 \qquad (392)$$

Dimethylformamide–dialkyl sulphate adducts react rapidly with various aliphatic and aromatic mono- and dicarboxylic acids to afford the corresponding esters (equation 393)[964].



Carboxylic acids are smoothly transformed into esters upon reaction with alkyl *t*-butyl ethers in the presence of proton-donating agents such as sulphuric acid or *p*-toluenesulphonic acid (equation 394)[632,966].

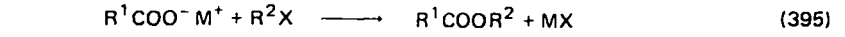


Trialkyl phosphites[965,966] can also serve as convenient esterifying agents, especially where strong acid catalysts are to be avoided.

Although several of the preceding methods can be used to prepare *t*-alkyl esters, the procedures employed most often consist of treatment of a carboxylic acid with an alkene in the presence of a strong mineral acid[967,968]. A recent synthesis of *t*-butyl esters involves reaction of the carboxylic acid with a mixture of isobutylene and *t*-butyl alcohol; the alcohol serves to prevent polymerization of the alkene during esterification[969].

2. *Alkylation of carboxylate salts*

Ester formation can be accomplished by treatment of carboxylate salts with a suitable alkylating agent as shown in equation (395). A number of satisfactory



procedures are available for accomplishing this type of esterification. The major differences between methods rest largely in the nature of the carboxylate salts and solvents employed. Alkyl halides and sulphonate esters are the most satisfactory alkylating agents. Dipolar, aprotic solvents such as DMF, DMAC, HMPA and DMSO accelerate the alkylations, but can be rather difficult to remove during isolation of the carboxylate ester. Most of the reactions listed in Table 42 proceed smoothly when the alkylating agent is primary, allylic or benzylic; however, elimination can become a serious side-reaction with secondary and tertiary alkylating agents. However, it has been found that mercury(II) acetate in diglyme reacts with *t*-butyl halides and α-phenylethyl chloride to afford the corresponding esters in the presence of triacyloxylboranes[999].

Phenacyl esters have been prepared in excellent yields by alkylation of carboxylate salts in the presence of catalytic amounts of crown ethers[1000]. The two-phase nature of these reactions makes product isolation quite convenient. Various diamines have also been found to activate carboxylate anions towards alkylation in two-phase media[1001].

Tetraalkylammonium carboxylates can be converted into esters by thermolysis in refluxing toluene[1002,1003]. Thus, phenyltrimethylammonium benzoate, prepared by titration of benzoic acid with trimethylanilinium hydroxide, affords methyl benzoate in 90% yield after brief refluxing in toluene (equation 396)[1002].

TABLE 42. Alkylations of carboxylate salts to form esters

Type of salt	Alkylating agent	Solvent	References
K^+, Na^+	RX	DMF	970–973
Na^+	MeI	DMAC	974
Na^+	EtI	Me_2CO	975
Na^+	RX	HOAc	976, 977
Na^+	$PhCH_2Cl$	EtOH	978
K^+, Na^+	Et_2SO_4	DMF, Me_2CO	979–981
Na^+	ROMs	DMF	982
K^+, Na^+	RX	HMPA	983–985
Na^+	$Et_3O^+BF_4^-$	H_2O	986
Ca^{2+}	MeI	DMSO	987
Ag^+	RX	Et_2O, HOAc	988–990
Cu^+	RX	C_6H_6, C_5H_5N	991–993
R_4N^+	RX	DMAC, DMF	994–996
R_4N^+	$Et_3O^+BF_4^-$	CH_2Cl_2	997
Hg^{2+}	RX	ROH/H_2O	998

Ion-exchange resins containing quaternary ammonium groups can be used to effect ester synthesis by first passing the carboxylic acid through the column to form the carboxylate resin (equation 397). Esterification is then achieved by

$$\text{Resin}-\overset{+}{\text{N}}\text{Me}_3\bar{\text{O}}\text{H} + \text{R}^1\text{COOH} \longrightarrow \text{Resin}-\overset{+}{\text{N}}\text{Me}_3\text{R}^1\text{COO}^- \xrightarrow{\text{R}^2\text{X}} \text{R}^1\text{COOR}^2 + \text{Resin}-\overset{+}{\text{N}}\text{Me}_3\text{X}^- \quad (397)$$

stirring the resin with an alkylating agent in a suitable solvent. The product is isolated simply by filtering off the resin and removing the solvent[1004].

Esters can be prepared by reaction of sodium carboxylates with alkylchlorosulphites (equation 398)[1005]. This reaction has recently been shown to proceed by initial formation of a mixture of dialkyl sulphite and anhydride, which then react further to produce the ester[1006].

$$\text{R}^1\text{COO}^-\text{Na}^+ + \text{ClSO}_2\text{R}^2 \xrightarrow{\Delta} \text{R}^1\text{COOR}^2 + \text{SO}_2 \quad (398)$$

3. Alcoholysis of acyl halides

Reaction of acyl chlorides with alcohols or phenols (equation 399) provides a method for ester synthesis which does not suffer from the reversibility found in direct esterification. In cases where the starting acid is insensitive to the reaction conditions necessary for acid chloride formation, this is often the method of choice for ester preparation.

$$\text{R}^1\text{COCl} + \text{R}^2\text{OH} \longrightarrow \text{R}^1\text{COOR}^2 + \text{HCl} \quad (399)$$

It is frequently advantageous to conduct these alcoholysis reactions in the presence of a base, especially when tertiary alcohols are used. This prevents conversion of the labile alcohol to the chloride and reduces the possibility of acid-catalysed decomposition of the resulting *t*-alkyl ester. Aqueous sodium or

potassium hydroxide, pyridine[1007], 2,6-lutidine[1008], dimethylaniline[1009-1011], tertiary aliphatic amines[1012-1015], tetramethylurea[1016], as well as magnesium[1017,1018] can be used as acid scavengers.

Secondary alcohols react smoothly with acid chlorides in HMPA[1019] and liquid sulphur dioxide[1020] to form the expected esters without added base. A general procedure which avoids the necessity of adding a basic reagent, and also activates the alcohol component of the reaction, consists of first converting the alcohol to its sodium or lithium alkoxide with sodium hydride[1021] or *n*-butyllithium[1022] in an inert solvent, and then adding the acyl or aroyl chloride (equation 400). Such

$$R^1COCl + R^2_3CO^-M^+ \longrightarrow R^1COOCR^2_3 + MCl \quad (400)$$

methods are especially useful for the preparation of esters from acid-sensitive alcohols. Thallium(I) salts of phenols are convenient intermediates for the synthesis of phenyl esters[1023]. Halomagnesium alkoxides react similarly with acid chlorides[1024].

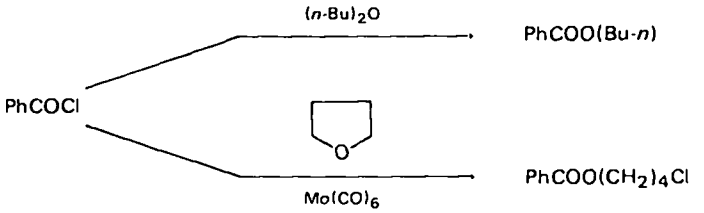
Addition complexes of acyl fluorides with antimony pentafluoride are highly reactive acylating agents which can be used to produce esters from alcohols and phenols (equation 401)[1025]. Acyl fluorides can be converted directly to esters by reduction with trialkylsilanes (equation 402)[1026]. Similar results are obtained with organotin hydrides[1027]. Reduction of acid chlorides with triphenyltin hydride in the presence of ketones can lead to direct production of secondary alkyl esters as shown in equation (403)[1028].

$$R^1CO^+\ SbF_6^- + R^2OH \xrightarrow{MeCN} R^1COOR^2 \quad (401)$$

$$2\ RCOF + 2\ Et_3SiH \longrightarrow RCOOR + 2\ Et_3SiF \quad (402)$$

$$EtCOCl + PhCOMe \xrightarrow[C_6H_6]{Ph_3SnH} EtCOO\overset{\displaystyle Me}{\underset{\displaystyle Ph}{\overset{|}{\underset{|}{CH}}}} \quad (403)$$

Acid chlorides react with ethers in the presence of Lewis acids[1029] or transition-metal carbonyls[1030,1031] to form esters in satisfactory yields (equation 404).



(404)

4. *Alcoholysis of anhydrides*

Anhydrides function as useful acylating reagents for the synthesis of esters from alcohols and phenols (equation 405). Generally, anhydrides are less reactive than

$$(R^1CO)_2O + R^2OH \longrightarrow R^1COOR^2 + R^1COOH \quad (405)$$

acyl halides in this capacity. With very reactive anhydrides such as trifluoroacetic anhydride, ester formation will occur rapidly in the absence of a catalyst. However, a variety of catalytic agents including sulphuric acid[1032], perchloric acid[1033], *p*-toluenesulphonic acid[1034], zinc chloride[1035,1036], sodium acetate[1037], sodium hydroxide[1038], tertiary aliphatic amines[1039] and pyridine[1040], have been employed. A combination of 4-dimethylaminopyridine and triethylamine is an especially effective catalyst[1041,1042]. As is the case with acid chlorides, alkoxides also react with anhydrides to produce esters[1043-1045]. Mixed anhydrides, prepared *in situ* from carboxylic acids and trifluoroacetic acid, react with various alcohols and phenols to afford numerous types of esters, including those as hindered as *t*-butyl mesitoate[1046]. Polymer-based anhydrides have recently been employed in the synthesis of benzoate esters[1047].

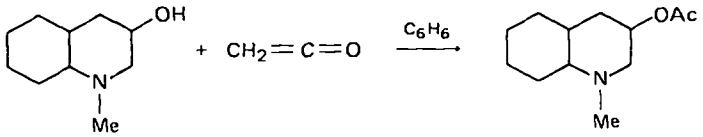
Acetic anhydride in the presence of ferric chloride reacts with a variety of ethers to form acetate esters (equation 406). Stereochemical results with optically active ethers suggest a dual mechanism involving *O*-acylation of the ether followed by dissociation of the more stable carbonium ion or displacement of an alkyl group by acetate[1048].

$$R^1-O-R^2 \xrightarrow[FeCl_3]{Ac_2O} R^1-\overset{+}{O}(C(=O)Me)-R^2 \xrightarrow[S_N2]{S_N1} MeCOOR^1 + MeCOOR^2 \qquad (406)$$

5. *Alcoholysis of ketenes*

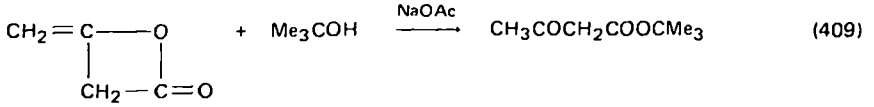
Ketenes react with alcohols and phenols to afford esters in an acylation process similar to those observed with acyl halides and anhydrides (equation 407). However, the procedure is used less frequently because ketenes are less readily available than the former reagents. The acylation of *N*-methyldecahydro-3-quinolinol is representative of such reactions (equation 408)[1049].

$$R^1C=C=O + R^2OH \longrightarrow R^1CHCOOR^2 \qquad (407)$$



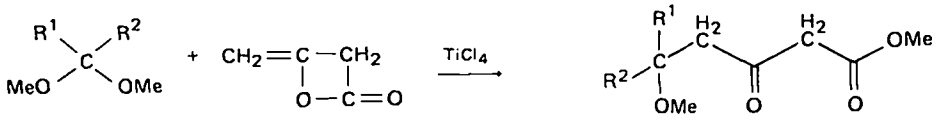
(408)

Diketene is a convenient reagent for the synthesis of β-keto esters possessing hindered alkoxy groups. Thus, *t*-butyl acetoacetate can be prepared from diketene and *t*-butyl alcohol (equation 409)[1050]. A recent paper describes a convenient procedure for carrying out these reactions in the presence of triethylamine[1051].



(409)

Diketene has been found to react with acetals in the presence of titanium(IV) chloride to afford δ-alkoxy-β-keto esters in good yields (equation 410)[1052]. Titanium(IV) ethoxide effects condensation of ketene with ketones to produce β-hydroxy esters (equation 411)[1053].



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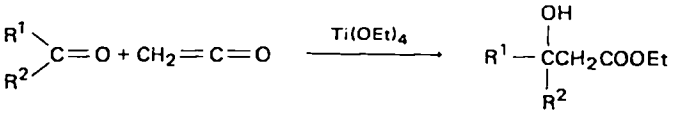
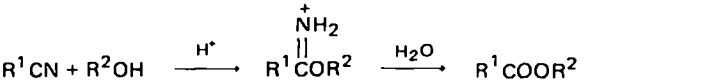


(411)

Ketene acetals[1054] and ketene thioacetals[1055] can be transformed into esters by acid-catalysed hydrolysis and alcoholysis, respectively.

6. *Alcoholysis of nitriles and amides*

Direct conversion of nitriles to esters can be accomplished without isolation of the intermediate acids. In most instances the cyano compound is first treated with an anhydrous alcohol in the presence of acid to form an imino ester, which is then hydrolysed to afford the desired ester (equation 412). The preparation of methyl 2,4,6-cycloheptatriene carboxylate[1056] may be viewed as representative of such reactions (equation 413). Additional details concerning the alcoholysis of nitriles may be found elsewhere[1057].



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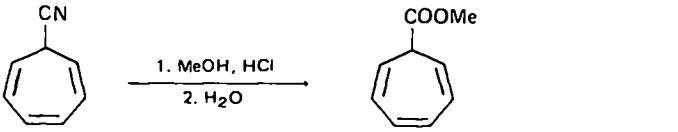
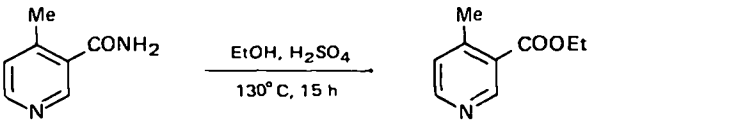


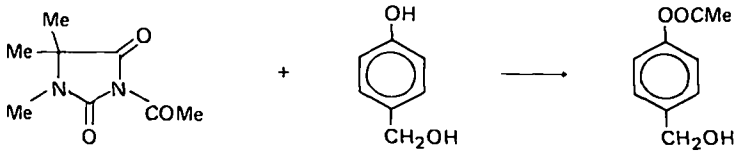
(413)

Alcoholysis of amides is encountered rather infrequently since it is much less facile than alcoholysis of more reactive acid derivatives. For example, conversion of benzamide to methyl benzoate requires prolonged treatment of the amide with methylpolyphosphate[1058] or methanol and boron trifluoride[1059] at relatively high temperatures. Preparation of ethyl 4-methylpyridine carboxylate from 4-methylnicotinamide by means of absolute ethanol and concentrated sulphuric acid also requires rather stringent conditions (equation 414)[1060].



(414)

Milder conditions can be used for alcoholysis if certain activated amides are employed. For instance, 3-acetyl-1,5,5-trimethylhydantoin reacts smoothly with *p*-hydroxybenzyl alcohol to afford the phenyl ester (equation 415)[1061]. It is interesting to note that the phenolic hydroxyl group reacts in preference to the alcohol function.



(415)

A convenient method for the synthesis of esters from secondary amides involves initial conversion of the amides into *N*-nitroso derivatives, which then undergo thermal elimination of nitrogen (equation 416)[1062,1063].

$$R^1CONHR^2 \xrightarrow[Ac_2O]{NaNO_2} R^1CON(NO)R^2 \xrightarrow{\Delta} R^1COOR^2 + N_2 \qquad (416)$$

Amides have also been reported to yield esters on treatment with alkyl halides and water[1064].

7. Transesterification

Two general types of transesterification procedures are employed in ester synthesis. In the first of these, an ester is allowed to react with an alcohol in the presence of an appropriate acidic or basic catalyst (equation 417). The equilibrium

$$R^1COOR^2 + R^3OH \underset{\text{or } B^-}{\overset{H^+}{\rightleftharpoons}} R^1COOR^3 + R^2OH \qquad (417)$$

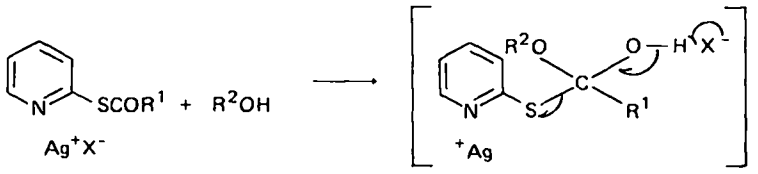
is shifted toward the desired ester by the use of excess alcohol and/or removal of one of the products by fractional distillation. Isopropenyl acetate is especially attractive as a source of acetate esters since acetone, formed as a by-product of the exchange, can be easily distilled from the reaction mixture[1065].

Common catalysts for transesterification include sulphuric[1066] and *p*-toluenesulphonic[1067] acids, as well as metal alkoxides[1067,1068]. More recently[1068], boron tribromide has been used to catalyse transesterification under mild conditions using both aliphatic alcohols and phenols. Among the newer examples of basic catalysts, tributyltin alkoxides[1069] and anion-exchange resins[1070] have been found to be effective. The latter reagents permit transesterification of esters of amino acids or peptides at room temperature. Transesterifications can also be accomplished in good yields by carrying out the reactions with potassium alkoxides in a Soxhlet apparatus containing molecular sieves to remove the displaced alcohol[1071].

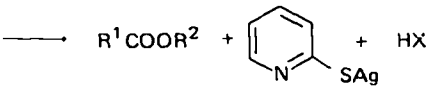
Potassium cyanide-catalysed transesterification appears to be the preferred method for unsaturated esters which are prone to undergo double-bond migration or *cis/trans* isomerization with strong acids and bases[1072].

A mild new method for ester synthesis based on transesterification consists of silver ion-induced reaction of alcohols with 2-pyridyl esters of thiocarboxylic acids (equation 418)[1073].

Transesterification can be carried out by allowing an ester to react with an excess of a free carboxylic acid (equation 419). This procedure may be viewed as an exchange of carboalkoxy groups between an ester and an acid. Thus, the alkoxy groups of the reactant and product esters are identical. This type of transesterification method is especially useful for the preparation of vinyl esters. Such reactions



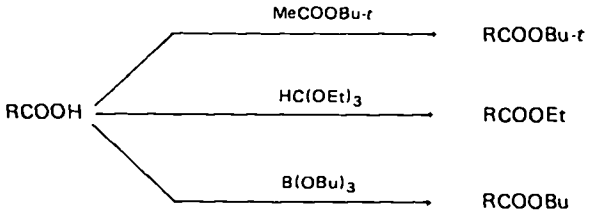
(418)



$$R^1COOR^2 + R^3COOH \longrightarrow R^3COOR^2 + R^1COOH \quad (419)$$

are usually catalysed by mercury(II) salts[1074,1075]. The synthesis of vinyl laurate[1074] from lauric acid and vinyl acetate may be taken as representative (equation 420). Isopropenyl acetate participates in similar reactions with carboxylic acids[1076]. *t*-Butyl acetate[1077], triethyl orthoformate[1078] and alkyl borates[1079] have been used in transesterifications as shown in equation (421).

$$CH_3(CH_2)_{10}COOH + CH_3COOCH{=}CH_2 \xrightarrow[H_2SO_4]{Hg(OAc)_2} CH_3(CH_2)_{10}COOCH{=}CH_2 + CH_3COOH \quad (420)$$



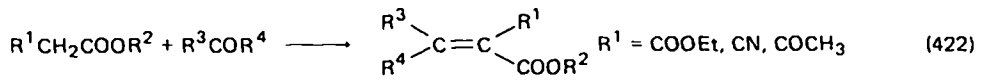
(421)

B. Esters by Condensation Reactions

Reactions involving carbanion intermediates play an important role in the synthesis of carboxylic acid esters. Many of the condensations discussed previously as routes to carboxylic acids can be adapted to the preparation of esters.

1. Knoevenagel reaction

This reaction involves treatment of an aldehyde or ketone with an active methylene compound in the presence of a catalytic amount of ammonia or an amine (primary or secondary) along with a small amount of a carboxylic acid (equation 422). If the active hydrogen component is diethyl malonate, ethyl

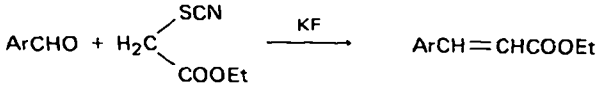


(422)

cyanoacetate or ethyl acetoacetate the product is an α,β-unsaturated ester. Malonic esters condense smoothly with aldehydes and reactive ketones such as acetone and

cyclohexanone; however, less reactive ketones require the more acidic substrate, ethyl cyanoacetate for successful formation of α,β-unsaturated esters. Numerous examples of ester syntheses may be found in the extensive review articles dealing with the Knoevenagel reaction[1080-1082].

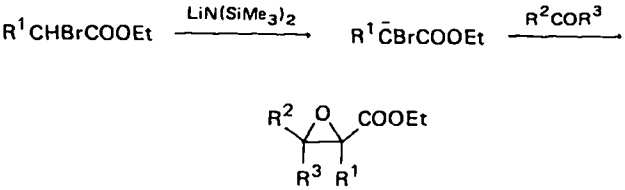
One of the most significant recent developments dealing with the Knoevenagel reaction is the finding that titanium chloride can serve as an effective catalyst for condensations involving both aldehydes and ketones[1083-1085]. Potassium fluoride has also been used in Knoevenagel-type condensations of aryl aldehydes with ethyl isothiocyanatoacetate[1086] to afford cinnamate esters (equation 423).



(423)

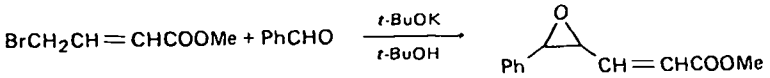
2. *Darzens reaction*

As a method for ester synthesis, the Darzens condensation finds its most frequent applications in the preparation of glycidic esters. Several recent observations concerning the Darzens reaction include the finding that lithium bis(trimethylsilyl)amide is an effective base for generating α-carbanions from α-bromo esters (equation 424)[1087]. A vinylogous counterpart of the normal Darzens con-



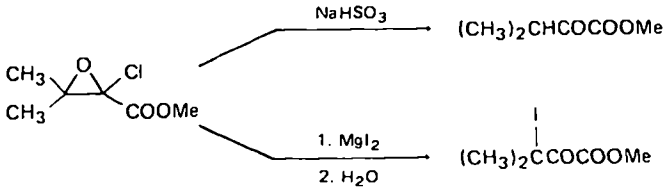
(424)

densation occurs when methyl 4-bromocrotonate is reacted with benzaldehyde in the presence of potassium *t*-butoxide (equation 425)[1088].



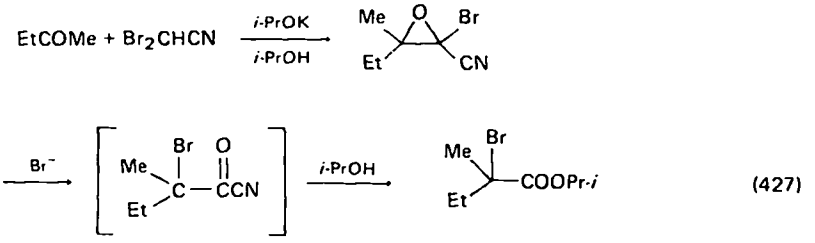
(425)

α-Chloroglycidic esters, prepared by Darzens condensations of aldehydes and ketones with α,α-dichloroacetates, can be converted to α-keto esters and β-iodo-α-keto esters by means of sodium bisulphite and magnesium iodide, respectively (equation 426)[1089].



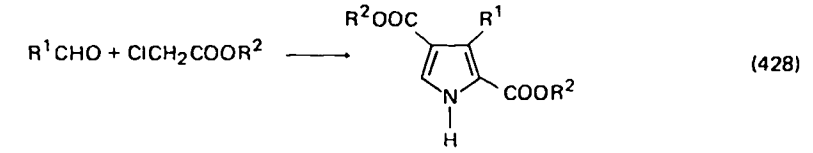
(426)

The synthesis of α-bromo esters can be accomplished through a Darzens-type condensation using dibromoacetonitrile as the active hydrogen component (equation 427)[1090].



(427)

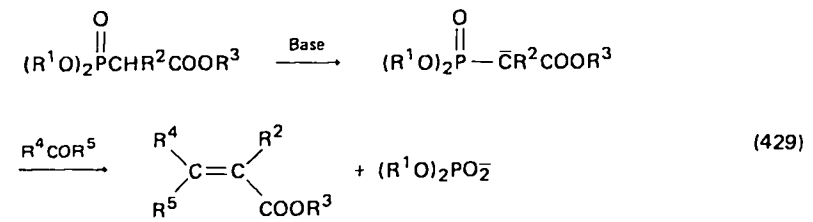
A new method for the preparation of 2,4-dicarboalkoxypyrroles involves Darzens condensation of α-chloro esters with aldehydes in the presence of 1,8-diazobicyclo-[5.4.0]undec-7-ene (equation 428)[1091].



(428)

3. *Wittig-type reactions*

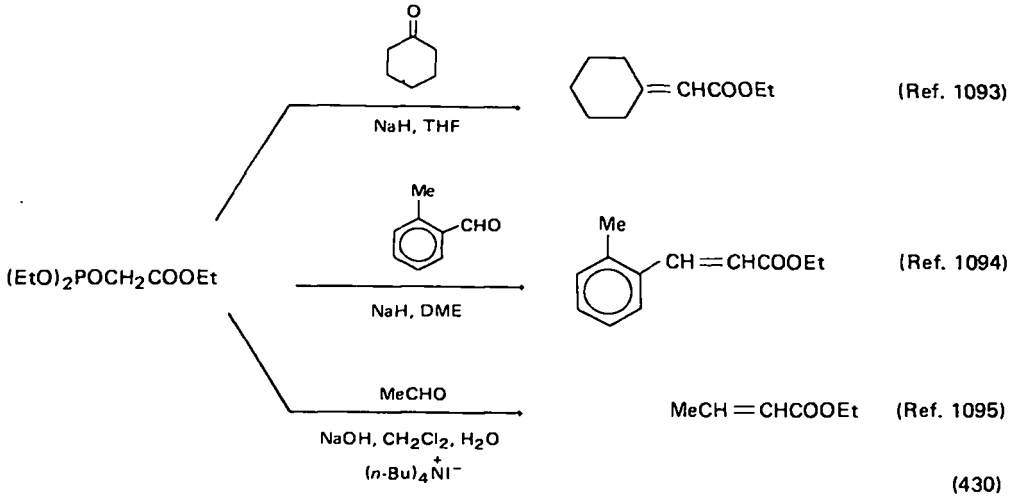
Among the various combinations of reactants which have been employed in Wittig-type syntheses of esters[125,126], the Wittig–Horner[1092] reaction is encountered most frequently because of its convenience and versatility. This reaction utilizes resonance-stablized carbanions derived from carboalkoxymethylphosphonate esters, which can then be reacted with aldehydes and ketones to produce α,β-unsaturated esters (equation 429). The reactions shown in equation (430) represent recent examples of the Wittig–Horner reaction using the carbanion derived from carboethoxymethyl diethylphosphonate. Numerous other well-tested examples of reactions employing this and related phosphonate carbanions in the synthesis of α,β-unsaturated esters are available[1096–1099].



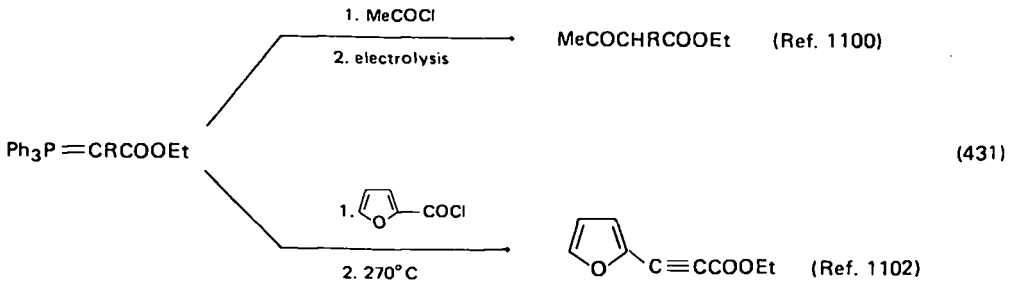
(429)

Carboalkyoxymethylenephosphoranes can be employed in the preparation of β-keto esters and α,β-acetylenic esters by first subjecting them to *C*-acylation with acid chlorides followed by electrolytic reduction[1100] and thermolysis[1101,1102], respectively (equation 431). Reactions with epoxides lead to α,β-unsaturated esters[1103].

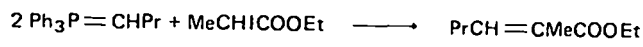
α, -Unsaturated esters can also be prepared by reacting α-bromo or α-iodo esters wit& two equivalents of a methylenephosphorane (equation 432)[1104]. In this case the alkylating agent, rather than the phosphonium ylide, provides the ester function.



(430)



(431)



(432)

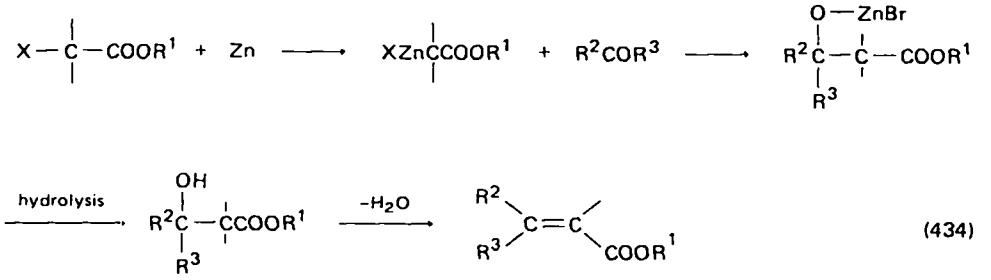
An attractive alternative to the Wittig–Horner reaction employs lithio salts of α-trimethylsilyl esters (equation 433)[1105-1107].

(433)

4. *Reformatsky reaction*

In the Reformatsky reaction an aldehyde or ketone is allowed to react with an α-halo ester in the presence of metallic zinc to afford a β-hydroxy ester. Dehydration of the hydroxy esters can be accomplished to afford α,β-unsaturated esters. This reaction (equation 434) has been reviewed extensively[1108-1110].

Improved yields in the Reformatsky reaction have been obtained recently by using a continuous-flow apparatus[1111] or activated zinc obtained by reduction of zinc chloride with potassium metal in THF[1112].

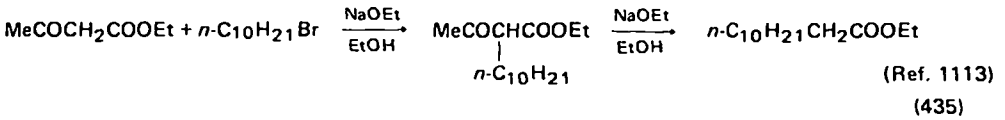


(434)

In connection with the use of the Reformatsky reaction as a synthetic route to β-hydroxy esters, it should be noted that reactions of carbonyl compounds with α-anions derived from esters provides a very attractive alternative, in that the α-anion method (Section III.B.7) can often be completed more quickly and in higher yields than the Reformatsky reaction.

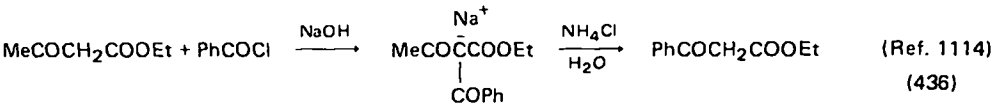
5. *Acetoacetic ester synthesis*

Ethyl acetoacetate is an important starting material for the synthesis of substituted acetate esters because of the ease with which alkylations can be effected at the active methylene position. Selective cleavage of the acetyl function completes the synthesis. It is important to prevent ester hydrolysis during acetyl cleavage, or the resulting β-keto acid may decarboxylate to generate ketonic products at the expense of ester formation. Ammonium hydroxide and alkali metal alkoxides are especially effective for this purpose. Reactions (435)–(437) are typical of acetoacetic ester syntheses of simple α-substituted acetates and β-keto esters.



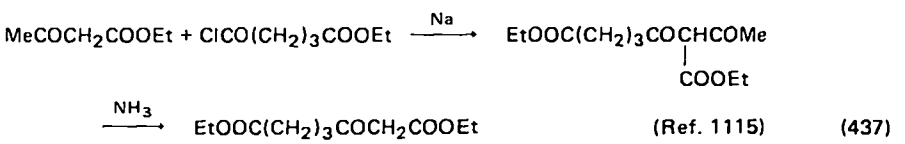
(Ref. 1113)

(435)



(Ref. 1114)

(436)

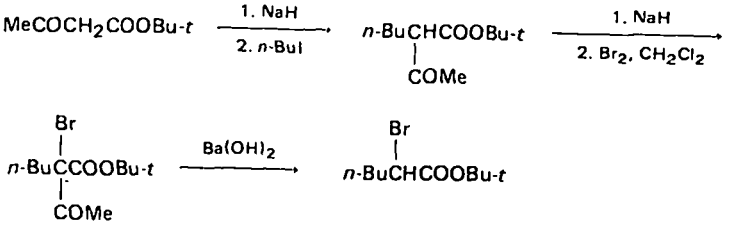


(Ref. 1115) (437)

α-Bromo esters can be prepared from *t*-butyl acetoacetate as shown in equation (438); acid-catalysed decomposition of the *t*-butyl ester gives the α-bromo acid[1116].

Reaction of *t*-butyl acetoacetate with *p*-toluenesulphonyl azide in the presence of triethylamine, followed by sodium methoxide-catalysed cleavage of the acetyl group affords *t*-butyl diazoacetate (equation 439)[1117].

The discovery[1118] that ethyl acetoacetate can be converted into its 1,3-dicarbanion by means of potassium amide in liquid ammonia has resulted in a number of



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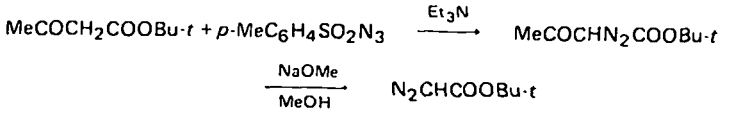
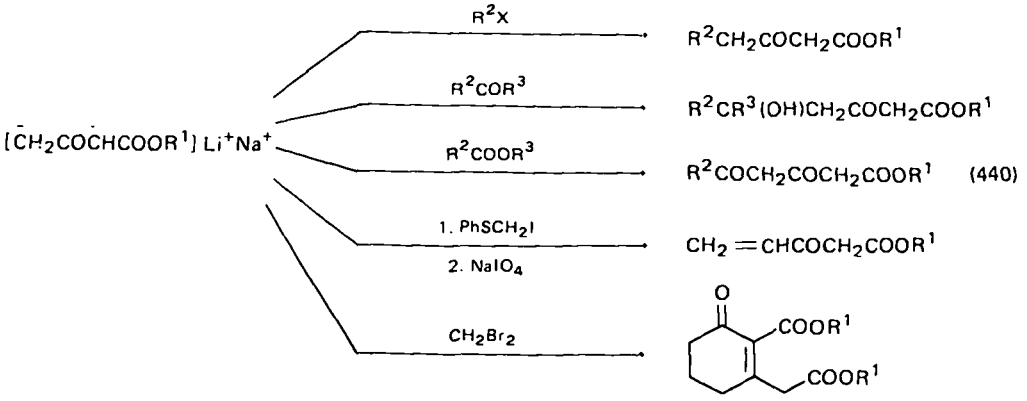


(439)

interesting new syntheses of β-keto esters based on condensation of this intermediate with electrophilic reagents (equation 440). The most satisfactory method



(440)

for dianion formation involves first treating ethyl acetoacetate with sodium hydride to generate the monoanion, and then adding an equivalent of *n*-butyllithium to remove a terminal methyl hydrogen[1119]. Reaction of the resulting sodiolithio salt with alkyl halides affords homologated β-keto esters resulting from alkylation at the original methyl group of the starting β-keto ester[1119]. Condensations with aldehydes and ketones produce δ-hydroxy-β-keto esters, which can be dehydrated to γ,δ-unsaturated β-keto esters[1120,1121]. Acylations with aromatic and aliphatic esters provide a route to β,δ-diketo esters[1122]. Treatment of the dianion of methyl acetoacetate with iodomethyl phenyl sulphide, followed by periodate oxidation of the resulting sulphide affords methyl 3-oxo-4-pentenoate[1123]. Alkylation of the same dianion with methylene bromide results in coupling, then intramolecular aldol condensations to give 2-carbomethoxy-3-carbomethoxymethyl-2-cyclohexanone[1124].

In connection with the utilization of β-keto esters as synthetic intermediates, it should be noted that methyl acetoacetate can be α-alkylated with allylic and benzylic halides under conditions of phase-transfer catalysis[1125], and with certain allyl ethers in the presence of sodium phenoxide and palladium(II) chloride complexes with triphenylphosphine[1126].

6. *Malonic ester synthesis*

As discussed earlier, the malonic ester synthesis is easily adapted to the preparation of various types of acids. However, the synthesis of simple esters is not so straightforward, since hydrolysis of substituted malonic esters generally results in cleavage of both ester groups to form malonic acids, which readily decarboxylate to give the appropriately substituted acetic acids. Therefore, in order to obtain esters as the ultimate products of a normal malonic ester synthesis, a final esterification step is required. This problem can be circumvented by several procedures which permit selective removal of one of the ester groups without affecting the other. The general approach is as shown in equation (441). Among the reagents which can be

$$CH_2(COOEt)_2 \xrightarrow[2.\ RX]{1.\ base} RCH(COOEt)_2 \longrightarrow RCH_2COOEt \qquad (441)$$

employed for monodecarboethoxylation of malonic esters are sodium chloride in aqueous DMSO[1127], and sodium cyanide in DMSO[1128]. Acylation of the lithium salt of ethyl trimethylsilylmalonate with α,β-unsaturated acid chlorides, followed by hydrolytic cleavage of the trimethylsilyl ester, gives unsaturated β-keto esters (equation 442)[1129]. An interesting new procedure for preparing simple esters

$$LiCH(COOSiMe_3)(COOEt) + CH_3CH{=}CHCOCl \xrightarrow[2.\ H_2O]{1.\ Et_2O,\ DME} CH_3CH{=}CHCOCH_2COOEt \qquad (442)$$

involves treatment of ethyl hydrogen malonate with two equivalents of lithium isopropylcyclohexylamide (LICA) to produce the dilithio salt (equation 443). Alkylation of the salt is then followed by decarboxylation to form α-substituted esters[1130].

$$H_2C(COOH)(COOEt) \xrightarrow{LICA} LiCH(COOLi)(COOEt) \xrightarrow[2.\ -CO_2]{1.\ RX} RCH_2COOEt \qquad (443)$$

α-Substituted acrylates can be prepared by Mannich condensations of monosubstituted malonic esters with dimethylamine, methylation of the resulting dimethylaminomethyl derivatives, and finally, decomposition of the resulting quaternary ammonium salts (equation 444)[1131].

$$RCH(COOMe)_2 \xrightarrow[2.\ MeI]{1.\ Me_2NH,\ HCHO} RC(COOMe)_2(CH_2\overset{+}{N}Me_3\ I^-) \xrightarrow[75^\circ C]{DMF} CH_2{=}CRCOOMe \qquad (444)$$

7. *From α-anions of esters*

Stoichiometric conversion of aliphatic esters to α-anions by simple acid–base reactions is often hampered by self-condensations or attack of the basic reagent at the carboalkoxy function. These problems can be overcome to some extent by using *t*-butyl esters with lithium amide in liquid ammonia as the base. Under these conditions, *t*-butyl acetate can be converted to its α-lithio salt in concentrations satisfactory for aldol condensations with various aldehydes and ketones to give β-hydroxy *t*-butyl esters (equation 445)[1132]. Other acetate esters also yield lithio salts, which react similarly with carbonyl compounds[1133–1137].

$$CH_3COOBu\text{-}t \xrightarrow[NH_3]{LiNH_2} LiCH_2COOBu\text{-}t \xrightarrow[2.\ H_2O]{1.\ R^1COR^2} R^1R^2C(OH)CH_2COOBu\text{-}t \quad (445)$$

The discovery that ethyl acetate, as well as numerous other aliphatic esters, can be converted quantitatively to α-lithio enolates by means of lithium bis(trimethylsilyl) amide[1138], lithium isopropylcyclohexylamide (LICA)[1139], or certain other lithium dialkyl amides in THF has resulted in the development of a number of new ester syntheses. The major advantages of these procedures are that they are easy to carry out and utilize readily available starting materials.

Alkylations[1140,1141] of ester enolates proceed readily to provide mono-, di- and trisubstituted acetates (equation 446), thereby presenting an attractive alternative to the malonic and acetoacetic ester syntheses. Lithio salts of α,β-unsaturated esters undergo alkylation at the α-position to give β,γ-unsaturated esters (equation 447)[1141,1142].

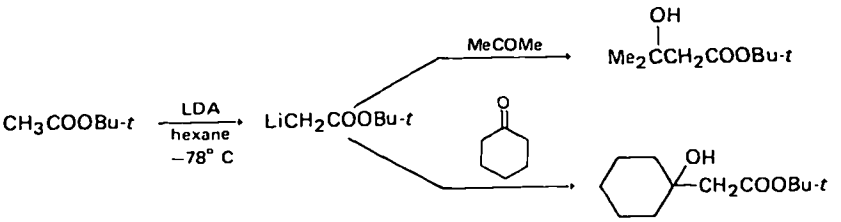
$$LiCH_2COOR^4 + R^1X \longrightarrow R^1CH_2COOR^4 \quad (446a)$$

$$R^1CHLiCOOR^4 + R^2X \longrightarrow R^1R^2CHCOOR^4 \quad (446b)$$

$$R^1R^2CLiCOOR^4 + R^3X \longrightarrow R^1R^2R^3CCOOR^4 \quad (446c)$$

$$CH_3CH{=}CHCOOEt \xrightarrow[2.\ MeI]{1.\ LDA} CH_2{=}CHCHMeCOOEt \quad (447)$$

Condensations of α-lithio esters, prepared in THF–hexane, with aldehydes and ketones afford β-hydroxy esters[1143–1145], in yields which surpass those obtained in Reformatsky reactions. An interesting example of such a reaction is found in the conversion of *t*-butyl acetate to its stable, crystalline lithium salt, which then reacts with acetone or cyclohexanone in toluene at 0°C to give the desired β-hydroxy ester in quantitative yield (equation 448)[1146].



(448)

β-Keto esters are available from ester enolates by reactions with acid chlorides (equation 449)[1147]. When the *O*-silyl ketene acetal prepared from lithio ethyl acetate and *t*-butyldimethylchlorosilane is allowed to react with acyl halides, β-keto esters are obtained upon hydrolysis with dilute hydrochloric acid (equation 450)[1148].

$$Me_2CHCOOEt \xrightarrow[2.\ PrCOCl]{1.\ LICA,\ -78°\ C} PrCOCMe_2COOEt \quad (449)$$

$$CH_2{=}C(OSiMe_2Bu\text{-}t)(OEt) \xrightarrow[2.\ H_3O^+]{1.\ RCOCl/Et_3N} RCOCH_2COOEt \quad (450)$$

α-Halo esters can be prepared by addition of ester enolates to THF solutions of iodine or bromine at −78°C (equation 451)[1149].

$$\text{LiCHBuCOOEt} + I_2 \xrightarrow[-78^\circ\text{C}]{\text{THF}} \text{BuCHICOOEt} \qquad (451)$$

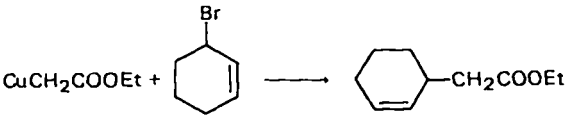
The synthesis of α-hydroxy esters from ester enolates can be accomplished by oxidation with molybdenum peroxide complexed with pyridine and hexamethylphosphoramide (HMPA) (equation 452)[1150]

$$R^1\text{CHLiCOOR}^2 \xrightarrow{MoO_5\cdot Py\cdot HMPA} R^1\text{CH(OH)COOR}^2 \qquad (452)$$

Reaction of lithio esters with copper(II) salts results in oxidative dimerization to afford succinate esters in yields of 20–95% (equation 453)[1151]. In a related

$$2\ \text{LiCCOOR} + 2\ CuBr_2 \xrightarrow[-78^\circ\text{C}]{\text{THF}} \text{ROOCC—CCOOR} \qquad (453)$$

process, it has been found that copper(I) ester enolates, prepared from the lithio salts and copper(I) iodide in THF, undergo dimerization on exposure to oxygen[1152]. These copper enolates also participate in coupling reactions with allylic halides to furnish γ,δ-unsaturated esters (equation 454).



(454)

α,β-Unsaturated esters can be synthesized from saturated esters by first preparing the lithium enolate, allowing it to react with dimethyl disulphide, oxidizing the resulting α-methylthio ester to the α-methylsulphinyl derivative, and then subjecting the sulphoxide to thermal elimination (equation 455)[1153].

$$\text{PrCHCH}_2\text{COOMe} \xrightarrow[\text{2. } Me_2S_2]{\text{1. LICA, THF, } -78^\circ\text{C}} \text{PrCHCHCOOMe} \xrightarrow[\text{MeOH, } H_2O]{NaIO_4}$$

(SMe on the α-carbon; Et)

$$\text{PrCHCHCOOMe} \xrightarrow[-\text{MeSOH}]{120^\circ\text{C}} \text{Pr, H, Et, COOMe (C=C)} \qquad \text{(Ref. 1153)} \qquad (455)$$

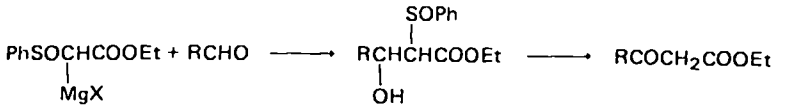
(SOMe on the α-carbon; Et)

In a related procedure, the carbanion derived from methyl α-phenylsulphinylacetate is alkylated, and the resulting α-alkyl derivatives are then subjected to elimination (equation 456)[1154]. The magnesium halide derivatives of ethyl

$$\text{PhSOCHCOOMe} + RCH_2X \xrightarrow{\text{HMPA}} \text{PhSOCHCOOMe} \xrightarrow{75-85^\circ\text{C}} \text{RCH=CHCOOMe} \qquad (456)$$

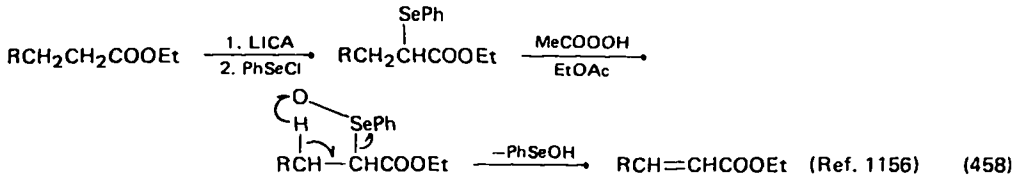
(CH2R on the α-carbon)

α-phenylsulphinylacetate react with aldehydes to give β-keto esters (equation 457)[1155].



(457)

Another procedure for synthesizing α,β-unsaturated esters involves reaction of ester enolates with phenylseleninyl chloride, followed by peroxy acid oxidation of the α-phenylseleno ester to the selenoxide, which spontaneously decomposes at room temperature to give the unsaturated ester (equation 458)[1156].

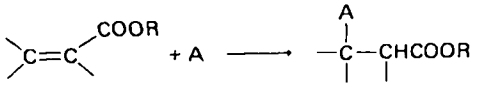


(458)

A recent publication summarizes reactions of ester enolates with various electrophiles, including most of those mentioned above[1157].

8. *Michael reactions and related conjugate additions*

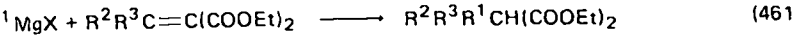
As a method for ester synthesis, the Michael reaction follows the same general patterns as outlined for the preparation of acids. Thus, if the acceptor is an α,β-unsaturated ester, conjugate addition of a nucleophilic addend (A) produces an ester elaborated at the β-position (equation 459). Alternatively, if the addend is the α-anion of a mono- or diester, and the acceptor contains an appropriate anion-stabilizing group (B), carbon–carbon bond formation occurs at the α-position of the ester (equation 460). Numerous examples of such reactions may be found in the previously cited reviews of the Michael reaction[192].



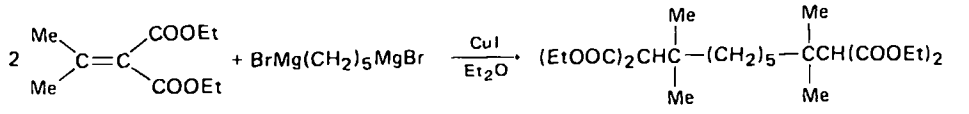
(459)

(460)

Conjugate additions of Grignard reagents to α,β-unsaturated esters, usually in the presence of copper(I) salts, is one of the most versatile methods for synthesizing β-substituted esters (equation 461)[1158]. In a recent report, bis-Grignard reagents have been found to react with two molecules of diethyl isopropylidenemalonate (equation 462)[1159].

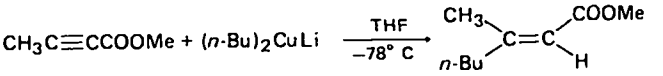


(461)



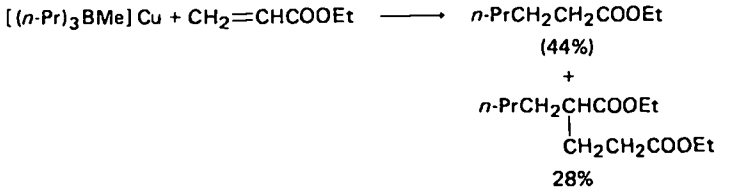
(462)

Conjugate addition of lithium dialkylcuprates or polymeric copper complexes to α,β-acetylenic esters can be used to prepare α,β-ethylenic esters in good yields and with a high degree of stereoselectivity[1160]. For example, lithium di-*n*-butylcuprate reacts with methyl 2-butynoate to give a 97 : 3 ratio of the *E* and *Z* isomers of methyl 3-methyl-2-heptenoate in 86% overall yield (equation 463)[1160]. Addition of copper allenes to methyl acetylenecarboxylate gives methyl esters of 2,4,5-heptatrienoic acid[1161].



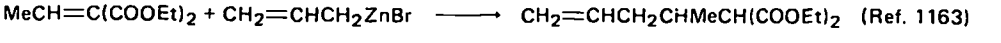
(463)

Although α,β-ethylenic esters which do not have a second electron-withdrawing substituent at the α-position tend to react sluggishly with organocopper reagents, certain cuprous methyltrialkylborates have been found to add to ethyl acrylate (equation 464)[1162].



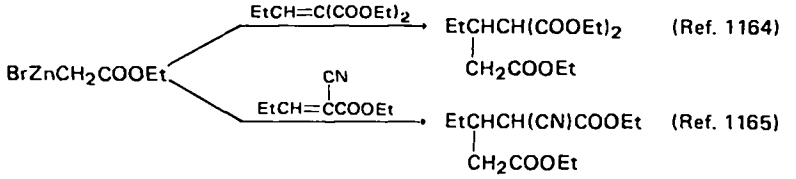
(464)

Allylzinc bromide participates in conjugate addition reactions with alkylidene malonates to produce unsaturated malonic esters (equation 465)[1163]. The Refor-



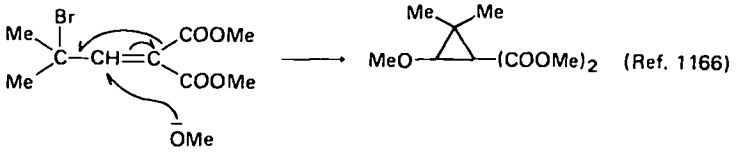
(465)

matsky reagent derived from ethyl bromoacetate adds to alkylidene malonates[1164] and alkylidenecyanoacetates[1165] (equation 466).



(466)

Nearly quantitative yields of methyl esters of 2,2,3-trisubstituted cyclopropanecarboxylic acids can be obtained as shown in equation (467)[1166].



(467)

9. *Claisen condensations*

The utility of the Claisen and Dieckmann reactions as methods for the synthesis of acyclic and cyclic β-keto esters is universally recognized. Both reactions have been reviewed[1167-1169].

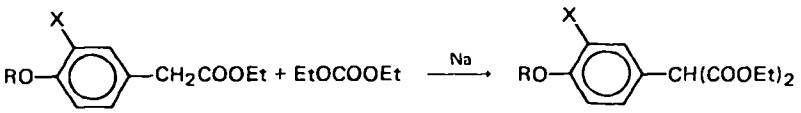
Simple Claisen condensations involve self-condensations of esters in the presence of a suitable basic reagent to afford β-keto esters (equation 468). When the ester to

$$R^1R^2CHCOOR^3 \rightleftharpoons R^1R^2\bar{C}COOR^3 \xrightleftharpoons{R^1R^2CHCOOR^3} R^1R^2CCOCHR^1R^2 \quad (468)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad COOR^3$$

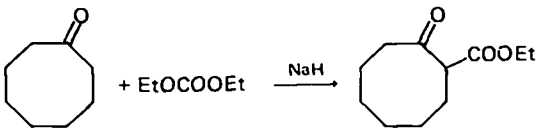
be employed has only one α-hydrogen the reaction proceeds poorly, because the desired β-keto ester lacks an ionizable methylene or methine hydrogen. Among the various basic reagents which have been employed in attempts to overcome this problem, potassium hydride now appears to be the most satisfactory and convenient for effecting self-condensation of α,α-disubstituted esters[1170].

Crossed Claisen condensations take two common forms, which can be used for the preparation of substituted malonic esters and β-keto esters, respectively. Thus, condensation of an ester possessing α-hydrogens with an oxalate or carbonate ester can afford substituted malonates. When a ketone is employed as the active hydrogen component with oxalates and/or carbonates, the product is a β-keto ester. These two procedures are especially valuable for preparing substituted malonic esters which cannot be synthesized by direct alkylation, and for synthesizing cyclic β-keto esters which cannot be obtained by Dieckmann reactions. These applications are illustrated in equations (469)--(471). Diethyl carbonate can also be used for introduction of a carboethoxy group into other types of active hydrogen substrates such as 2,6-lutidine[1174].

$$PhCH_2COOEt + (COOEt)_2 \xrightarrow[2.\ \Delta,\ -CO]{1.\ NaOEt} PhCH(COOEt)_2 \quad \text{(Ref. 1171)} \quad (469)$$



(Ref. 1172) (470)



(Ref. 1173) (471)

C. Esters by Free-radical Processes

1. *Radical additions and substitution reactions*

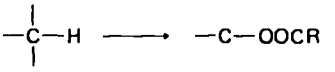
Carboalkoxylalkyl (—C—COOR) residues can be introduced into unsaturated substrates by means of the same type of radical-addition processes (equation 472)

$$R^1CH{=}CH_2 + \underset{\displaystyle |}{\overset{\displaystyle H}{\overset{|}{C}}}COOR^2 \xrightarrow[\text{initiator}]{\text{radical}} R^1CH_2CH_2\underset{\displaystyle |}{\overset{\displaystyle |}{C}}COOR^2 \quad (472)$$

which have been outlined for introduction of carboxyalkyl residues (Section II.C). Direct aromatic substitution by carboalkoxyalkyl radicals is encountered less frequently than radical additions to unsaturated systems.

2. *Acyloxylation reactions*

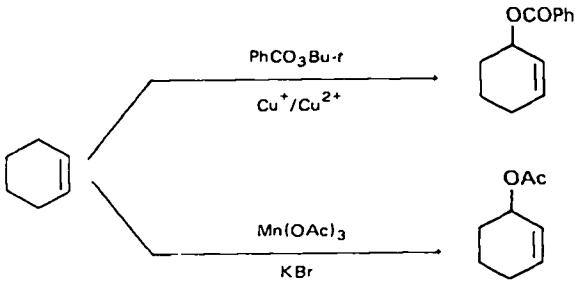
Acyloxylation can involve direct substitution of an acyloxy (RCOO—) function for a hydrogen attached to carbon (equation 473). These reactions often occur in



(473)

good yields when the hydrogen to be replaced is allylic, benzylic, or adjacent to a carbonyl, ether or thioether function. Reagents which furnish the acyloxy group include peroxy esters in the presence of transition-metal ions, carboxylic acids in the presence of hydroperoxides or dialkyl peroxides, peroxy acids, diacyl and diaroyl peroxides, and metal salts such as lead(IV) acetate, mercury(II) acetate, thallium(III) acetate and palladium(II) acetate.

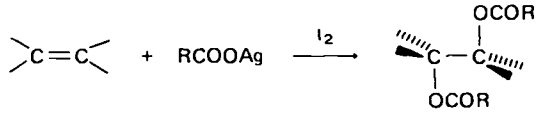
Acyloxylations at carbon by means of peroxides and metal salts have been reviewed recently[1175-1177]. Reactions (474) and (475) are representative of this



synthetic approach. A recent report claims high yields of phenylacetates from acetoxylation of substituted benzenes with palladium(II) acetate[1179]. The acetoxy group is introduced *meta* to most substituents. Lead(IV) trifluoroacetate has been used for trifluoroacetoxylation of aromatic substrates[1180,1181]. With compounds containing a trimethylsilyl group, introduction of the acyloxy group occurs by displacement of the trimethylsilyl moiety[1179]. Benzoyloxylation at the 5-position of certain pyrimidines by means of benzoyl peroxide has been reported[1182]. Substitutive acetoxylation of vinyl carbon has been accomplished using lead(II) acetate[1183].

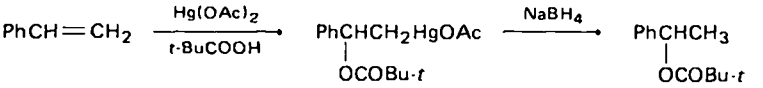
Esters can also be synthesized by acyloxylation reactions in which introduction of the RCOO— group is effected by addition to the multiple bond of unsaturated substrate rather than by substitution at an allylic position. Unlike the substitutive acyloxylations, these reactions do not necessarily involve free radicals. The Prevost reaction[1184-1186], in which an olefin is allowed to react with two equivalents of a

silver carboxylate in the presence of an equivalent of iodine (equation 476), represents an example of such a reaction. Thallium(I) carboxylates in the presence



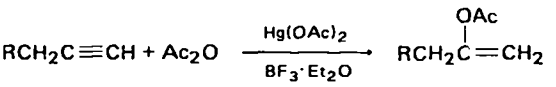
(476)

of iodine behave similarly to produce β-iodoalkyl carboxylates[1187]. Mercury(II) acetate adds to olefins to form acyloxy mercuriacetates, which can then be reduced with sodium borohydride to provide the desired ester (equation 477)[1188]. Re-



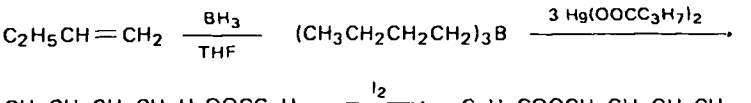
(477)

action of acetylenes with acetic anhydride in the presence of boron trifluoride etherate and a catalytic amount of mercury(II) acetate affords alkenyl acetates in good yields (equation 478)[1189].



(478)

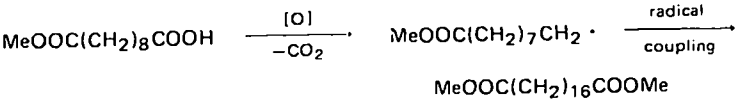
Although the acyloxylations of olefins described above involve Markownikoff addition of the carboxylic acid to alkenes and alkynes, a new procedure has been developed for anti-Markownikoff esterification of olefins. This method involves hydroboration of the alkene, followed by reaction of the resulting trialkylborane with a mercuric carboxylate to form a primary alkylmercuric carboxylate, which is then treated with iodine to give a primary ester. The synthesis of *n*-butyl butyrate from 1-butene illustrates the reaction scheme (equation 479)[1190].



(479)

3. *Anodic dimerization*

Kolbe electrolysis of half-esters of dicarboxylic acids is a useful route to symmetrical dicarboxylic acid esters (equation 480). This reaction, which has been



(480)

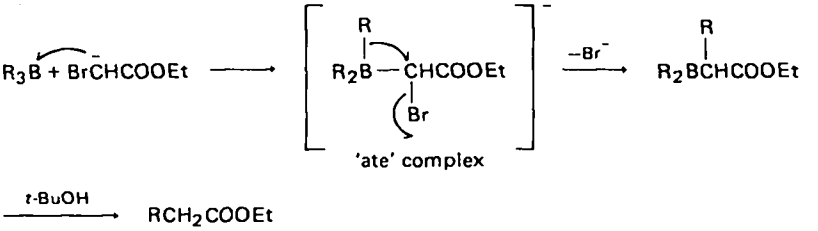
discussed in detail elsewhere[1191-1193], involves electrochemical oxidation of half-esters at a platinum anode to generate ω-carboalkoxy radicals, which then undergo dimerization to form the desired diesters. Related reactions involving radical intermediates formed in electrolytic oxidations of acids have been reviewed[1194].

D. Miscellaneous Ester Syntheses

1. *From organoboranes*

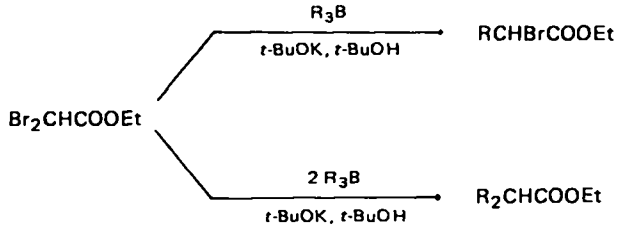
Organoboranes[1195] can be employed in several general types of ester syntheses. In each of these methods the boranes react with various classes of esters to effect elaboration of the original ester structure.

Reactions of α-bromo esters with trialkylboranes in the presence of potassium *t*-butoxide in *t*-butyl alcohol results in introduction of an alkyl group in place of the α-bromine (equation 481)[1196]. This α-alkylation presumably involves initial

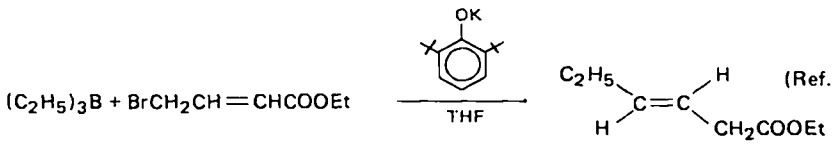


(481)

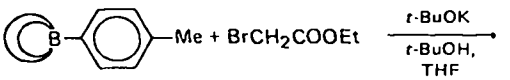
formation of an 'ate' complex from the α-bromo carbanion of the ester and the trialkylborane. Migration of an alkyl group from boron to carbon is accompanied by loss of bromide ion to give a new trialkylborane, in which one of the alkyl residues is an α-alkylacetate moiety. Cleavage of the α-carbon–boron bond is then effected by *t*-butyl alcohol to afford α-alkylacetates. Improvements in the original procedure include the use of potassium 2,6-di-*t*-butylphenoxide[1197,1198] as the basic reagent and β-alkyl- and β-aryl-9-borabicyclo[3.3.1]nonanes as the source of the alkyl or aryl group[1199]. If dihalo esters are used it is possible to prepare α-bromo esters or α,α-dialkyl esters by varying the amount of organoboranes (equation 482)[1200]. Equations (483) and (484) illustrate several additional appli-



(482)



(Ref. 1201) (483)

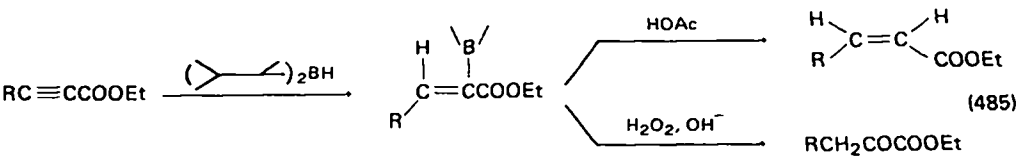


(Ref. 1202) (484)

cations of this α-alkylation method to the synthesis of esters. The organoborane alkylation procedure complements other methods such as the malonic ester syn-

thesis and alkylation of α-anions in that it allows facile introduction of highly-branched alkyl substituents as well as aryl groups.

Stereoselective synthesis of (*Z*)-α, -unsaturated esters can be accomplished by addition of disiamylborane to α,β-acetylenic esters followed by protonolysis. When the adduct is oxidized with alkaline hydrogen peroxide, α-keto esters are produced (equation 485)[1203].

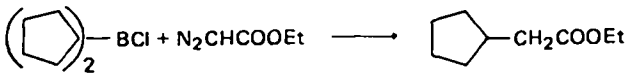


(485)

Trialkylboranes react with ethyl diazoacetate to provide α-substituted acetates (equation 486)[1204]. Introduction of bulky alkyl groups is accomplished more

$$R_3B + N_2CHCOOEt \xrightarrow[2.\ H_2O]{1.\ THF} RCH_2COOEt \qquad (486)$$

efficiently with dialkylchloroboranes (equation 487)[1205]. α-Bromo esters can be prepared by reaction of trialkylboranes with ethyl diazoacetate followed by addition of *N*-bromosuccinimide to the reaction mixture (equation 488)[1206].

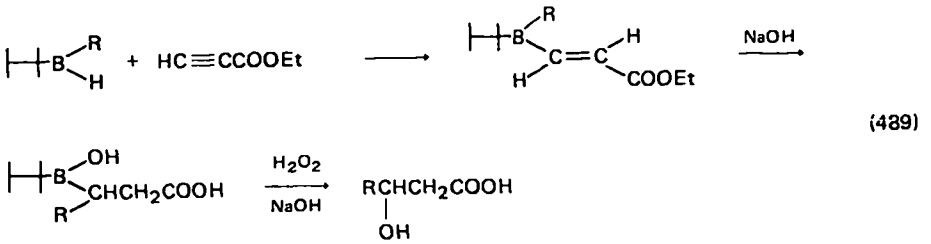


(487)

$$N_2CHCOOEt \xrightarrow[2.\ NBS]{1.\ (C_2H_5)_3B} C_2H_5CHBrCOOEt \qquad (488)$$

Trialkynylboranes also react with ethyl diazoacetate to form β,γ-acetylenic esters in excellent yields[1207].

Treatment of ethyl propiolate with thexylmonoalkylboranes leads to initial hydroboration of the triple bond. Subsequent reaction of the resulting alkenylborane with hydroxide ion leads to alkyl-group migration. Hydrolysis with aqueous hydrogen peroxide then affords β-hydroxy acids (equation 489)[1208].



(489)

2. *From acetylenes*

Alkali-metal salts of ethoxyacetylene can be alkylated with alkyl halides and the 1-ethoxyethynyl portion of the resulting acetylene then converted to a carboethoxymethylene group upon mercuric oxide-catalysed hydration of the triple bond (equation 490)[1209]. Thus, ethoxyacetylene serves as a two-carbon homolo-

$$EtOC{\equiv}CNa + BuBr \xrightarrow{NH_3} BuC{\equiv}COEt \xrightarrow[H_2SO_4]{HgO} BuCH_2COOEt \qquad (490)$$

gating agent in ester preparation. More recently[1210], it has been found that 1-ethoxyvinyl esters, obtained by mercuric ion-catalysed addition of carboxylic acids to ethoxyacetylene, can be converted to β-keto esters upon treatment with zinc salts (equation 491). This reaction scheme is equivalent to acylation and

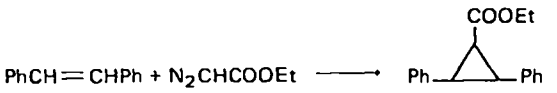
$$EtOC{\equiv}CH + RCOOH \xrightarrow{Hg^{2+}} RCOOC(OEt){=}CH_2 \xrightarrow[2.\ H_3O^+]{1.\ Zn^{2+}} RCOCH_2COOEt \qquad (491)$$

hydration of ethoxyacetylene. Terminal acetylenes have recently been converted to α-keto esters by ozonization in methanol (equation 492). 1-Bromoacetylenes undergo a similar conversion when potassium iodide is added to the reaction mixture after treatment with ozone[618].

$$RC{\equiv}CH \xrightarrow[2.\ SOCl_2]{1.\ O_3,\ MeOH} RCOCOOMe \qquad (492)$$

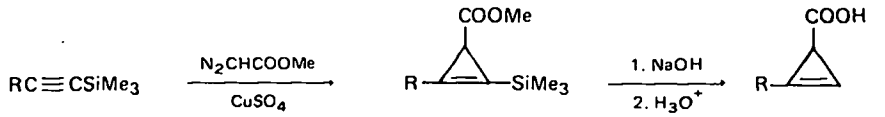
3. *From diazo esters*

The utility of ethyl diazoacetate in ester synthesis was demonstrated earlier in reactions involving organoboranes. In addition to these reactions, ethyl diazoacetate can be employed in the preparation of cyclopropanecarboxylic acids and esters as shown in the reaction with stilbene (equation 493)[1211]. Cyclopropenecarboxylic



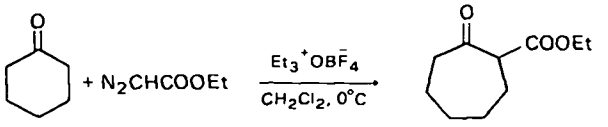
(493)

acids can be prepared in an anologous manner from 1-trimethylsilylacetylenes (equation 494)[1212]. When ethyl diazoacetate is allowed to react with both cyclic



(494)

and acyclic ketones in the presence of triethyloxonium fluoroborate, ring expansion or one-carbon homologation takes place to form β-keto esters (equation 495)[1213]. The preparations and reactions of diazo esters have been reviewed[1214,1215].



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IV. SYNTHESIS OF ACID ANHYDRIDES

The most frequently employed methods for synthesizing carboxylic acid anhydrides involve dehydrative coupling of acids, acylation of carboxylate salts with acyl halides, reactions of acids with dissimilar anhydrides in a type of anhydride interchange, and reactions of acids with ketene. Cyclic anhydrides of various types are often prepared by Diels–Alder reactions of maleic anhydride with dienes[11,1216]. All of these methods, along with several more specialized procedures have been discussed in recent reviews[1217,1218]. The synthetic methods described in this section represent newer procedures in the areas of dehydrative coupling of carboxylic acids and acylation of carboxylate salts.

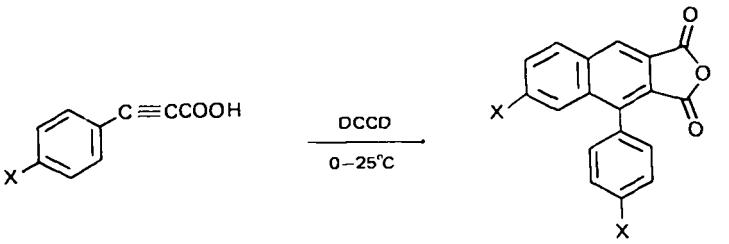
A. Dehydrative Coupling of Carboxylic Acids

These reactions are represented by the general equation (496) in which two molecules of acid react to form an anhydride and a molecule of water. Actually

$$2\ RCOOH \longrightarrow (RCO)_2O + H_2O \qquad (496)$$

such dehydrations are used mainly to prepare cyclic anhydrides from dibasic acids. Acyclic acids seldom undergo purely thermal anhydride formation. Consequently, acyclic anhydrides are prepared through reactions of this type by adding an appropriate reagent, which reacts with the free carboxyl group of the acid to produce an activated derivative. The activated acid is then attacked by the weakly nucleophilic oxygen of a free acid molecule to produce an anhydride. This approach allows the conversion of carboxylic acids into anhydrides to be accomplished under mild conditions.

Various carboxylic acids yield symmetrical anhydrides upon treatment with dicyclohexylcarbodiimide (DCCD)[1219,1220] or ethoxyacetylene[1221–1223]. It has been found that insoluble polystyrene polymer containing carbodiimide residues can be employed to effect anhydride formation from acetic, stearic and glutaric acids[1224]. Phenylpropiolic acids undergo an unusual cyclodimerization in the presence of DCCD to form 1-phenylnaphthalene-2,3-dicarboxylic anhydrides (equation 497)[1225]. Ynamines are claimed to be superior to DCCD and ethoxy-



(497)

acetylene for dehydrative coupling of acids[1226]. Other reagents which are satisfactory for dehydration of acids include iodosobenzene[1227], trisdimethylamino phosphine[1228], chlorotrisdimethylaminophosphonium perchlorate[1229], triphenylphosphine dibromide[1230], cyanogen bromide[1231] and phenylisocyanate[1232].

Reaction of mono- and dicarboxylic acids with thionyl chloride has been reinvestigated as a method for preparing symmetrical anhydrides[1233]. In contrast to earlier reports, anhydrides were found to form readily without the need for

added pyridine. Thionyl bromide has been employed as a dehydrating agent to produce cyclic anhydrides[1234].

B. Acylation of Carboxylate Salts

This classical procedure for synthesizing anhydrides consists of treatment of alkali metal, silver or thallium(I) carboxylates with an acyl chloride (equation 498).

$$R^1COOM + R^2COCl \longrightarrow R^1COOCOR^2 + MCl \quad (498)$$

This method has a decided advantage over dehydrative coupling in that unsymmetrical anhydrides are readily synthesized.

A convenient method for the preparation of symmetrical aromatic acid anhydrides consists of treatment of an aromatic acid chloride with aqueous sodium bicarbonate containing catalytic amounts of pyridine (equation 499)[1235].

$$ArCOCl \xrightarrow[\text{pyridine, } 20^\circ C]{NaHCO_3} ArCOOCOAr \quad (499)$$

Reaction of silver or mercury(I) carboxylates with *N,N'*-dicyclohexylthiourea at room temperature in acetone, chloroform or acetonitrile, constitutes a useful method for the preparation of anhydrides from acid salts (equation 500)[1236]. This

$$2\ RCOOAg + C_6H_{11}NHC(=S)NHC_6H_{11} \longrightarrow RCOOCOR + Ag_2S + C_6H_{11}NHC(=O)NHC_6H_{11} \quad (500)$$

procedure bears a resemblance to an older method in which silver benzoate was converted to benzoic anhydride by means of carbon disulphide[1237].

α-Oxo sulphoxides, obtained by oxidation of thiol esters with *N*-bromosuccinimide, react with sodium salts of carboxylic acids to afford anhydrides (equation 501)[1238].

$$R^1C(=O)S(=O)R^2 + R^3COONa \longrightarrow R^1COOCOR^3 \quad (501)$$

V. SYNTHESIS OF ACYL HALIDES

Preparations of acyl halides have been reviewed in a previous volume of this series published in 1972[1239]. For the sake of consistency we have followed, where appropriate, the general format of this earlier review in presenting more recent developments in the field of acyl halide synthesis.

A. From Carboxylic Acids and Anhydrides

In addition to the common halogenating agents such as thionyl chloride, phosphorus halides, carbonyl halides and sulphonyl halides, several new reagents have been found to be effective for converting acids and/or anhydrides into acyl halides.

Acyl chlorides can be prepared in good yields under mild conditions by reaction of carboxylic acids with trialkyl- or triarylphosphines in carbon tetrachloride (equation 502). This procedure is very attractive for acid-sensitive carboxylic acids,

$$RCOOH + Ph_3P + CCl_4 \longrightarrow RCOCl + Ph_3PO + CHCl_3 \quad (502)$$

as no hydrogen chloride is produced during the reaction[1240]. However, one disadvantage is the bothersome separation of triphenylphosphine oxide from the desired acyl chloride. This can be avoided by employing a polymer-supported triphenylphosphine[1241]. With such reagents the phosphine oxide function remains attached to the polymer framework, and can be removed by filtration (equation 503).

$$\text{Polymer}-PPh_2 + RCOOH + CCl_4 \longrightarrow RCOCl + \text{Polymer}-POPh_2 + CHCl_3 \quad (503)$$

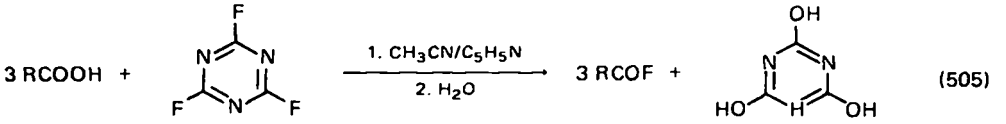
A procedure related to the polymer-supported triphenylphosphine method utilizes trisubstituted phosphine dichloride groupings chemically bonded to cross-linked polystyrene beads (equation 504). The recovered polymeric phosphine

$$\text{Polymer}-CH_2PPh_2(Cl)_2 + RCOOH \xrightarrow{COCl_2} RCOCl + \text{Polymer}-CH_2POPh_2 + HCl \quad (504)$$

oxides can be reconverted to the original phosphine dichlorides by treatment with phosgene[1242].

Phosgene continues to be a useful and economical reagent for large-scale production of acyl chlorides from both acids and anhydrides. Recent studies have shown that phosgene functions best when used in the presence of nitrogen-containing catalysts such as imidazole[1243], DMF[1244] and caprolactam[1245].

Several less traditional reagents have been used for the conversion of acids to acyl chlorides. These include sulphur monochloride[1246], a mixture of sulphur dichloride and chlorine[1247] and phosphosalicylic halides[1248]. Reaction of carboxylic acids with hydrogen chloride and ethyl isocyanate in ethereal solution at room temperature affords acid chlorides in good yields.



(505)

Acyl bromides can be prepared from carboxylic acids by reaction with thionyl bromide[1249] or by adding bromine to a mixture of the acid and phosphorus tribromide[1250].

Several new methods for direct preparation of acyl fluorides have appeared recently. Cyanuric fluoride is a mild reagent suitable for the preparation of acyl fluorides from acids containing unsaturation, hydroxyl groups or aromatic rings[1251]. Dialkylaminosulphur trifluorides[1252] and selenium tetrafluoride[1253] can be used to prepare acyl fluorides from acids. The latter reagent also reacts with anhydrides to give acyl fluorides, while the former reacts with acyl chlorides to afford fluorides by halogen exchange[1254]. Reaction of benzoyl chloride with hydrogen fluoride to give benzoyl fluoride is typical of standard exchange procedures for acyl fluoride preparation[1255].

Although thionyl chloride is often the reagent of choice for preparing acyl chlorides from carboxylic acids, several undesirable side-reactions can take place

depending upon reaction conditions and the method of product isolation. For example, thionyl chloride in the presence of catalytic amounts of pyridine has been shown to afford mainly α-chloro-α-chlorosulphenylacyl chlorides (equation 506)[1256,1257]. In a related reaction, chlorosulphonylalkanoyl chlorides are pro-

$$RCH_2COOH + SOCl_2 \xrightarrow{C_5H_5N} \begin{matrix} Cl \\ | \\ RCCOCl \\ | \\ SCl \end{matrix} \qquad (506)$$

duced in good yields on treatment of alkanoic acids with chlorosulphonic acid or a mixture of sulphur trioxide and phosphorus oxychloride (equation 507)[1258].

$$R^1R^2CHCOOH + SO_3 + POCl_3 \longrightarrow R^1R^2C\begin{matrix} COCl \\ SO_2Cl \end{matrix} \qquad (507)$$

Previous reports that aromatic acids which contain electron-withdrawing substituents cannot be satisfactorily converted to acyl chlorides by means of thionyl chloride have been disproved by the synthesis of 4-nitrobenzoyl chloride[1259]. Reinvestigation of the reaction of phenylmalonic acid with thionyl chloride has revealed that chlorocarbonyl ketenes can be prepared by this reaction if the crude product is refluxed in toluene or xylene prior to final distillation (equation 508)[1260].

$$RCH(COOH)_2 \xrightarrow{SOCl_2} RCH(COCl)_2 \xrightarrow[\Delta]{-HCl} RC\begin{matrix} =C=O \\ COCl \end{matrix} \qquad (508)$$

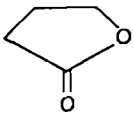
B. From Esters

Esters and lactones can be cleaved to form acyl halides by treatment with triphenylphosphine dihalides (equation 509) or a mixture of triphenylphosphine

$$R^1COOR^2 + Ph_3PX_2 \longrightarrow R^1COX + R^2X + Ph_3PO \qquad (509)$$

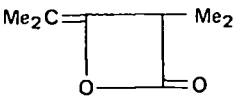
dichloride and boron trifluoride[1261,1262]. Esters of halogenated acids are cleaved in refluxing acetonitrile, whereas unsubstituted esters require higher temperature. Phenyl esters do not react with these reagents.

Thionyl chloride and zinc chloride can be used to produce γ-chlorobutryoyl chloride from butyrolactone (equation 510)[1263]. 3-Hydroxy-2,2,4,3-pentenoic



$$+ SOCl_2 + ZnCl_2 \longrightarrow Cl(CH_2)_3COCl \qquad (510)$$

acid β-lactone is similarly converted to 2,2,4-trimethyl-3-oxovaleryl chloride with zinc chloride and anhydrous hydrogen chloride (equation 511)[1264].



$$\xrightarrow[ZnCl_2]{HCl} Me_2CHCOCMe_2COCl \qquad (511)$$

Trimethylsilyl esters are converted to acid chlorides by thionyl chloride[1265]. Isopropenyl esters afford acyl fluorides on treatment with hydrogen fluoride[1266].

C. From Trihalides

Trichloromethyl arenes can serve as useful precursors to aroyl chlorides (equation 512). Several new methods are available for accomplishing such conversions.

$$ArCCl_3 \longrightarrow ArCOCl \qquad (512)$$

For example, benzotrichlorides react with sulphur dioxide above 150°C to form benzoyl chlorides and thionyl chloride[1267]. Lewis-acid catalysts allow these reactions to proceed at lower temperatures. Bis(trichloromethyl)arenes are converted to diacid chlorides under these reaction conditions. Trichloromethylarenes also yield aroyl chlorides on treatment with sulphur trioxide at 25–50°C[1268]. Toluene, benzyl chloride and benzal chloride, as well as a number of their substituted derivatives, react with thionyl chloride above 200°C to yield benzoyl chlorides.

Conversion of aliphatic trichlorides into acyl chlorides is encountered infrequently. However, a new synthesis of *t*-butoxycarbonyl fluoride involves initial transformation of fluorotrichloromethane into carbonyl chloride–fluoride, which is subsequently reacted with *t*-butyl alcohol to give the carbonyl fluoride (equation 513)[1270].

$$Cl_3CF \xrightarrow[SO_3]{H_2SO_4} ClCOF \xrightarrow[Et_3N]{t\text{-BuOH}} t\text{-BuOCOF} \qquad (513)$$

D. By Carbonylation

Benzylic halides undergo carbonylation with carbon monoxide in the presence of chlorocarbonyl-bis(triphenylphosphine)rhodium to form phenylacetyl halides (equation 514)[1271,1272]. Carbonylation of allylic halides affords unsaturated acyl

$$ArCH_2X + CO \xrightarrow[150°C,\ 150\ kg/cm^2]{Ph_3P(CO)Cl} ArCH_2COX \qquad (514)$$

halides with carbon monoxide over a palladium or rhodium catalyst at 100–150°C and 3000 psi[1273].

Olefinic substrates can be carbonylated in the presence of hydrogen chloride using ligand-stablized palladium(II), tin(II) or germanium(II) chlorides. Thus, reaction of 1-heptene under these conditions gives octanoyl chloride (equation 515)[1274]. Dinuclear metal carbonyl compounds such as cobalt octacarbonyl

$$CH_3(CH_2)_4CH{=}CH_2 + CO + HCl \xrightarrow[90°C,\ 3000\ psi]{PdCl_2(PPh_3)_2} CH_3(CH_2)_4CH_2CH_2COCl \qquad (515)$$

catalysed the carbonylation of olefins in carbon tetrachloride solution to give 2-alkyl-4,4,4-trichlorobutanoyl chlorides[1275,1276]. Here again, reaction conditions are rather stringent, with temperatures ranging from 50–130°C and carbon monoxide pressures of 60–200 atm.

In a reaction which may be regarded as analogous to carbonylation, phosgene undergoes 1,2-addition with alkynes in ether at low temperature to produce

3-alkylthio-3-chloroacryloyl chlorides in moderate to good yields (equation 516)[1277].

$$R^1SC{\equiv}CR^2 + COCl_2 \longrightarrow \begin{matrix} R^1S & & R^2 \\ & C{=}C & \\ Cl & & COCl \end{matrix} \qquad (516)$$

Benzoyl fluoride and terephtaloyl fluoride can be prepared from arenesulphonyl fluorides, or from arenesulphonyl chlorides and sodium fluoride, by treatment with carbon monoxide in the presence of palladium (equation 517)[1278].

$$ArSO_2F + CO \xrightarrow[>200^\circ C,\ 100\ atm]{Pd} ArCOF + SO_2 \qquad (517)$$

E. Miscellaneous Methods

Aryl aldehydes are chlorinated to form aroyl chlorides by means of sulphur monochloride in the presence of catalytic amounts of DMF (equation 518)[1279].

$$ArCHO + S_2Cl_2 \xrightarrow[40-90^\circ C]{DMF} ArCOCl \qquad (518)$$

Δ^2-Alkenoic acid chlorides are available by allowing ketene to react with boron trichloride adducts of aldehydes and ketones (equation 519)[1280].

$$R^1COR^2 + CH_2{=}C{=}O \xrightarrow[ether]{BCl_3} R^1R^2C{=}CHCOCl \qquad (519)$$

VI. SYNTHESIS OF AMIDES

Most of the important methods of amide synthesis reported in the chemical literature through 1971 have been reviewed[1281-1284]. Consequently, emphasis here is directed toward procedures which have appeared since then.

A. Amides by Acylation Reactions

Acylations of ammonia and amines with carboxylic acids and acid derivatives constitute the most important class of reactions leading to amides (equation 520).

$$R^1COX + HN\!\!<\!\!\!> \longrightarrow R^1CON\!\!<\!\!\!> + HX$$

$$X = OH, \text{halogen}, R^2COO, R^2O \qquad (520)$$

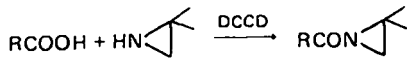
Acyl halides and anhydrides are used most frequently because they are more reactive toward nitrogen nucleophiles than are acids and esters. The following syntheses are categorized in terms of the type of acylating reagent employed.

1. Acylations with carboxylic acids

Prior to the discovery of reagents which can catalyse the acylation of amines with free carboxylic acids, amide formation was usually accomplished by thermo-

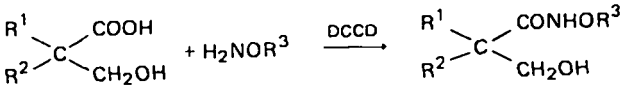
lysis of ammonium carboxylates. Such conditions are often unsatisfactory, as in the formation of peptide bonds from stereochemically labile amino acids. A review of coupling reagents which activate the carboxyl group of free acids toward reactions with amine nucleophiles has appeared recently[1285].

Dicyclohexylcarbodiimide (DCCD) continues to be among the most popular and useful reagents for amide formation from free acids. For example, *N*-acylaziridines, which serve as useful intermediates for the preparation of 2-oxazolines, can be prepared using DCCD (equation 521)[1286]. Similarly, *N*-hydroxy- and *N*-alkoxy-



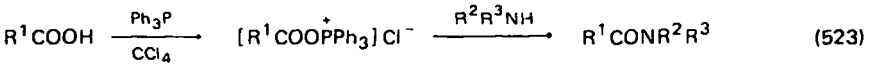
(521)

3-hydroxypropanamides are obtained by reaction of DCCD or diisopropylcarbodiimide with 3-hydroxypropanoic acids and hydroxylamine or its *O*-alkyl derivatives (equation 522)[1287].



(522)

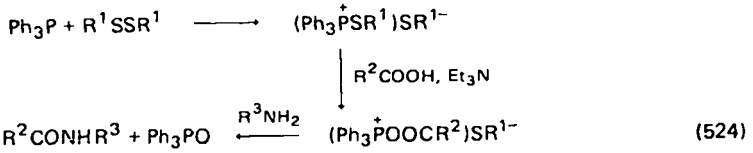
Several organophosphorus reagents have been employed in amide formation. Reaction of carboxylic acids with the complex formed from triphenylphosphine and carbon tetrachloride affords triphenylacyloxyphosphonium chlorides, which in turn react with various primary and secondary amines to produce the desired amides (equation 523)[1288]. Trisdimethylamino phosphine can be used in place of



(523)

triphenylphosphine[1228]. As mentioned earlier[1228], if the amine is omitted, anhydrides are produced in reactions involving these phosphine reagents. Triphenylphosphite in combination with imidazole promotes formation of steroidal amides from the free acids[1289,1290]. Amides can also be prepared from carboxylic acids and amines using phosphorus acid or its mono-, di- or triesters in the presence of pyridine and iodine or bromine as an oxidizing agent[948,949]. This procedure is also useful for esterification of carboxylic acids if alcohols are added to the reaction mixture in place of amines.

Treatment of carboxylic acids or *N*-protected amino acids with simple amines or free amino-acid esters in the presence of a mixture consisting of triphenylphosphine, dichlorodiphenyl disulphide, triethylamine and copper(II) chloride affords simple amides or peptides in high yields (equation 524)[1291]. The reaction is



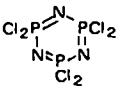
(524)

assumed to proceed through initial formation of a phosphonium salt via reaction of triphenylphosphine with the disulphide. This salt then reacts with the carboxylic acid to form a phosphonium carboxylate, which in turn effects acylation of the

amine or amino-acid ester to produce the observed amide or peptide. The sulphide by-product is removed as its copper(II) salt. Amides and peptides are available in good yields from carboxylic acids and amines using diethyl phosphorocyanidate as the coupling agent (equation 525)[1292]. Acyl cyanides appear to be the reactive

$$R^1COOH + R^2R^3NH \xrightarrow[Et_3N]{NCP(O)(OEt)_2} R^1CONR^2R^3 \qquad (525)$$

intermediates in these acylations. Hexachlorocyclotriphosphatriazine (equation 526)[1293] and triphenylphosphonium triflate[950] have also been used to effect



$$R^1COOH + R^2NH_2 \longrightarrow R^1CONHR^2 \qquad (526)$$

amide formation. The latter reagent is also an efficient promoter of ester formation.

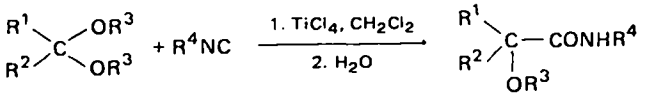
Silicon tetrachloride has attracted considerable attention as a coupling reagent for amide formation[1294]. Condensations of *N*-protected amino acids with amino-acid esters proceed best with this reagent if the acid is first converted to the tetraacyloxysilane (equation 527)[1295].

$$R^1NHCH_2COOH \xrightarrow[pyridine]{SiCl_4} (R^1NHCH_2COO)_4Si \xrightarrow{H_2NCH_2COOR^2} R^1NHCH_2CONHCH_2COOR^2 \qquad (527)$$

Carboxylic acids and amines react at room temperature in the presence of stoichiometric amounts of titanium(IV) chloride to form amides as shown in the production of *N*-ethylformamide (equation 528)[1296]. Titanium(IV) chloride also

$$2\,HCOOH + 6\,EtNH_2 + TiCl_4 \longrightarrow 2\,HCONHEt + 4\,EtNH_3Cl + TiO_2 \qquad (528)$$

catalyses the formation of 2-alkoxyalkanamides from acetals and isocyanides by activating the acetals toward nucleophilic attack by the isocyanides (equation 529)[1297].



(529)

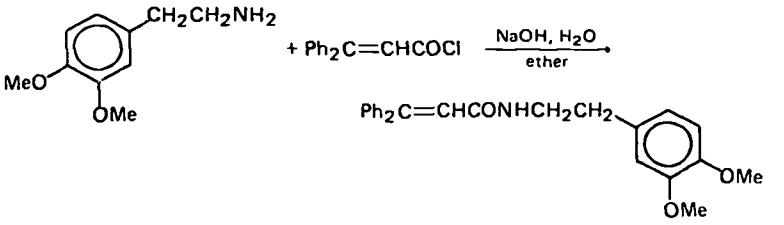
Attempts to develop satisfactory boron reagents for amide and peptide syntheses led to the discovery that trimethoxyborane in the presence of catalytic amounts of *p*-toluenesulphonic acid was suitable for the preparation of simple amides, but unsatisfactory for the synthesis of peptides[1298]. Recently, boron trifluoride etherate has been found to function as an effective reagent for amidation of carboxylic acids. Reactions are conducted by simply refluxing an acid and amine in benzene or toluene in the presence of triethylamine[1299].

Several coupling reagents which are useful for esterification of acids can also be employed for amide synthesis if an amine is used in place of an alcohol or phenol. *N*-Methyl-2-halopyridinium iodides[958], β-trichloromethyl-β-propiolactone[953], *N*,*N*′-carbonyldiimidazole[954] and certain allenic sulphonium salts[1300] fall into this category.

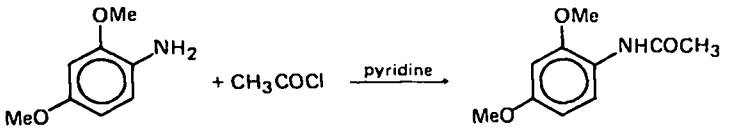
2. *Acylations with acyl halides*

Acylation of ammonia or primary and secondary amines with acid chlorides is probably the most frequently employed method of amide preparation. However, this route suffers from some marked disadvantages, especially with carboxylic acids which are sensitive to reagents required for their conversion to acyl halides.

General experimental procedures usually involve reaction of the acyl halide with an excess of an appropriate amine, or with a molar equivalent of the amine to be acylated, along with an excess of a tertiary amine or alkali metal hydroxide to absorb the acid formed during acylation. The reactions shown in equations (530)–(532) are representative of recent examples of amide formation from acyl



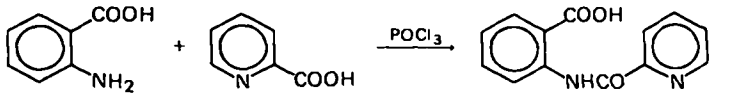
(Ref. 1301) (530)



(Ref. 1302) (531)

$$2\,CH_3NH_2 + (CH_3)_3CH(CH_2)_2COCl \xrightarrow{ether} (CH_3)_2CH(CH_2)_2CONHCH_3$$ (Ref. 1303) (532)

halides. An interesting example of amine acylation by an acid chloride is found in the synthesis of 2-picolinolylaminobenzoic acid, which is accomplished by dropwise addition of phosphorus oxychloride to a mixture of anthranilic acid and 2-picolinic acid in toluene (equation 533)[1304].



(533)

In some instances acylations can be accompanied by loss of a substituent other than hydrogen from the amino nitrogen. Thus, silyl-protected secondary amines lose the trialkylsilyl grouping upon treatment with acid chlorides (equation 534)[1305].

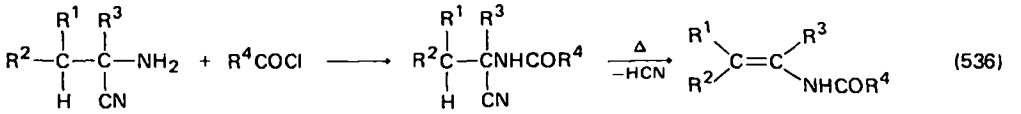
$$PhCH_2NMeSi(Et)_3 + CH_3COCl \xrightarrow{n\text{-hexane}} PhCH_2NMeCOCH_3 + Et_3SiCl$$ (534)

Reaction of tertiary methylamines with 2,2,2-trichloroethyl chloroformate affords the corresponding demethylated trichlorocarbamates in excellent yields (equation 535). The carbamates can subsequently be reduced with zinc in acetic

$$R^1R^2NCH_3 + Cl_3CCH_2OCOCl \xrightarrow{benzene} R^1R^2NCOOCH_2CCl_3 \xrightarrow[HOAc]{Zn} R^1R^2NH$$ (535)

acid or methanol to afford secondary amines. This procedure represents a convenient new method for amine demethylation[1306].

Enamides can be synthesized by acylation of 2-aminonitriles with acid chlorides followed by thermal dehydrocyanation of the resulting 2-acylaminonitriles (equation 536)[1307].



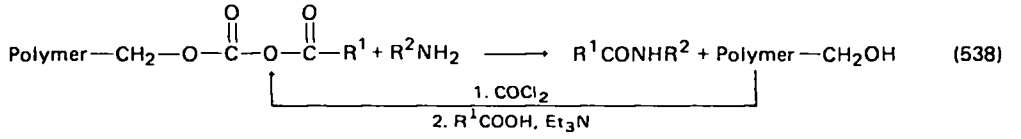
(536)

3. Acylations with anhydrides

Ammonolysis and aminolysis of carboxylic acid anhydrides are quite similar to acylations involving acid halides, Numerous examples of such reactions may be found in the cited review articles dealing with preparations of amides. Among the more interesting recent findings in this area of synthesis is the discovery that tertiary amines undergo dealkylative acylation with acetic anhydride at reflux (equation 537)[1308]. The alkyl groups expelled most easily are *t*-butyl, benzyl, α-phenylethyl, diphenylmethyl and trityl.

(537)

Polymeric anhydrides, prepared from chloromethylated polystyrene, react with aliphatic and aromatic primary amines to produce amides. The resulting hydroxymethylated polymer, can be reconverted to the polymeric anhydride by treatment with phosgene, followed by reaction with an appropriate carboxylic acid and triethylamine (equation 538)[1309].



(538)

4. Acylations with esters

As would be anticipated, esters are less reactive acylating reagents than acyl halides and anhydrides. Phenyl formate, does however, react rapidly with primary aliphatic and aromatic amines to afford *N*-substituted formamides (equation 539)[1310]. D-Glucosamine is readily acylated by means of *p*-nitrophenyl esters in

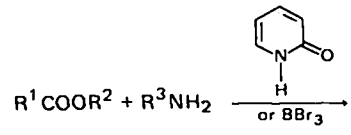
(539)

DMSO[1311]. Less reactive esters usually require catalysts in order to serve as useful acylating agents.

2-Pyridone has been shown to be effective in promoting reactions between various aliphatic amines and non-activated esters[1312]; more recently, boron tribromide has been used to effect amination of esters[1313] (equation 540).

1,1-Dicyanoethyl acetate, prepared from acetic anhydride and cyanide ion, is a useful activated ester, which reacts rapidly with amines to form *N*-substituted

acetamides in excellent yields (equation 541)[1314]. Another class of activated esters, 2-phenyl-3-(acyloximino)-3*H*-indoles, react readily with amines to give carboxamides (equation 542)[1315].



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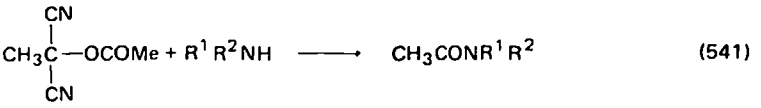

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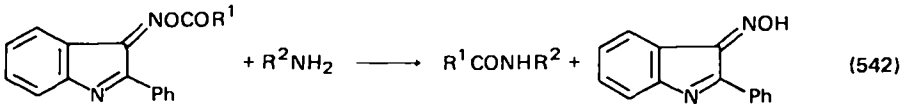
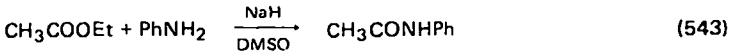


(542)

Conversion of amines to alkali-metal salts, which are then allowed to react with an appropriate ester to form amides, has been accomplished with lithium aluminium hydride[1316], *n*-butyllithium[1317] and sodium hydride[1318] (equations 543 and 544).



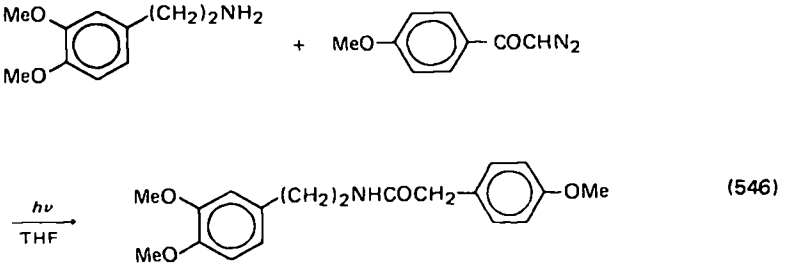
(543)

(544)

5. *Acylations with ketenes and isocyanates*

Ketene reacts smoothly with primary and secondary amines to form acetamides. Ketene acylations are used less frequently than those involving the more readily accessible acid halides and anhydrides. However, with acid-sensitive amines such acylations can be attractive. Reaction of β-methylallylamine with ketene is representative of amide formation[1319]. Acylations of amino alcohols with ketenes show a high degree of selectivity, giving rise to exclusive formation of *N*-acyl derivatives[1320]. Photolysis of mixtures of amines and diazo ketones provides a useful method of amide synthesis (equation 546). Photolytic decomposition of the diazo ketone produces a substituted ketene, which reacts with the amine[1321].

(545)



(546)

Isocyanates react with Grignard reagents (equation 547) and organolithium reagents to form amides[1322]. The required isocyanates can be prepared by Curtius reaction of acid chlorides with sodium azide. Amide formation is then accomplished by addition of the crude isocyanate to an ethereal solution of an appropriate lithium reagent (equation 548). The generality of this reaction scheme has been demonstrated with various acid chlorides and methyl-, *n*-butyl-, and phenyllithium[1323].

$$R^1N{=}C{=}O + R^2MgX \longrightarrow R^2CONHR^1 \tag{547}$$

$$R^1COCl \xrightarrow[\Delta]{1.\ NaN_3} R^1N{=}C{=}O \xrightarrow[2.\ H_3O^+]{1.\ R^2Li} R^1NHCOR^2 \tag{548}$$

Treatment of trimethylsilyl isocyanate or chloroacetyl isocyanate with Grignard reagents in dioxan at low temperature affords primary amides in good yields (equations 549 and 550). The trimethylsilyl group is cleaved during aqueous workup, while sodium methoxide is required to remove the chloroacetyl function[1324].

$$Me_3SiN{=}C{=}O \xrightarrow{R^1MgX} [Me_3SiNHCOR^1] \xrightarrow[NH_4Cl]{H_2O} R^1CONH_2 \tag{549}$$

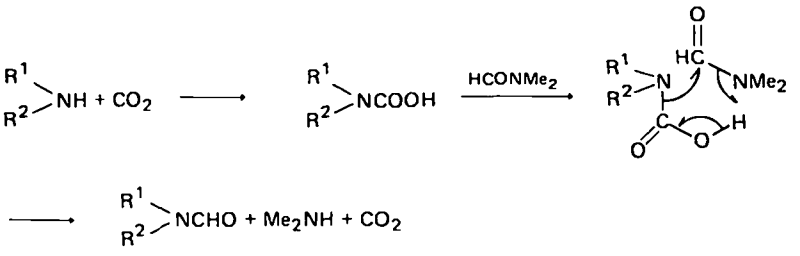
$$ClCH_2CON{=}C{=}O \xrightarrow{R^1MgX} [ClCH_2CONHCOR^1] \xrightarrow[MeOH]{MeONa} R^1CONH_2 \tag{550}$$

6. *Transamidation*

Reaction of carboxamides with amines can result in transfer of the acyl group of the amide to the nitrogen of the amine. In such cases the amide acts as the acylating

$$R^1CONR^2R^3 + HNR^4R^5 \longrightarrow R^1CONR^4R^5 + R^2R^3NH \tag{551}$$

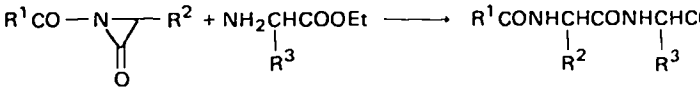
agent. Formylation of aliphatic amines with DMF takes place in the presence of carbon dioxide to afford *N*-alkylformamides[1325]. Cyanoacetamide also participates to transfer a cyanoacetyl group, while acetamide reacts poorly and *N,N*-dimethylacetamide (DMAC) fails to react. Aromatic amines are not acylated by this procedure. The mechanism of transacylation is assumed to involve initial reaction of the amine with carbon dioxide to produce the corresponding carbamic acid, which then reacts with DMF to form the observed product and expel carbon dioxide (equation 552).



(552)

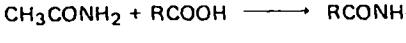
More recently it has been found that aliphatic amines undergo both uncatalysed and acid-catalysed acylations with formamide, DMF and DMAC[1326]. Although aromatic amines again fail to react under these conditions, base-catalysed formylation of aromatic amines can be accomplished with DMF[1318].

N-acylaziridones react with ethyl esters of amino acids in a novel transamidation process leading to peptides (equation 553)[1327].



(553)

In a somewhat different type of transamidation, acetamide has been reported to react with aliphatic acids at elevated temperatures to give moderate yields of primary amides (equation 554)[1328]. Similarly, *N*-formylpiperidine reacts with fatty acids to afford *N*-acylpiperidides (equation 555)[1329]. Treatment of DMF at



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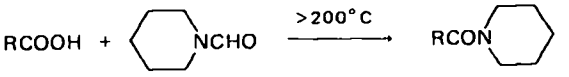


(555)

reflux with carboxylic acids in the presence of phosphorus pentoxide leads to formation of *N,N*-dimethyl carboxamides[1330]. Reactions of carboxylic acids with bis(diethylamino)sulphoxide in benzene gives rise to *N,N*-diethyl carboxamides (equation 556)[1331].

(556)

B. Amides by Hydrolysis and Cleavage Reactions

1. Hydrolysis of nitriles

Hydrolysis of nitriles to amides has long been recognized as a useful synthetic procedure (equation 557). The hydrolysis may be arrested at the intermediate

(557)

amide stage by using concentrated sulphuric acid, basic hydrogen peroxide, polyphosphoric acid or boron trifluoride[1332]. However, since none of these methods has been found to be universally acceptable for aliphatic and unsaturated nitriles in particular, the search for new catalysts and milder reaction conditions has continued.

Several modifications of traditional hydrolytic methods have proved effective for nitrile hydrolysis. The sulphuric acid method of hydrolysis has been conducted in sulphur trioxide while continuously adding just enough water to convert the sulphur trioxide to 100% sulphuric acid. This procedure appears to be generally satisfactory for hydrolysing unsaturated nitriles, such as methacrylonitrile[1333]. Aromatic nitriles are readily converted to the corresponding amides by reaction at 40°C with 30% methanolic hydrogen peroxide containing potassium bicarbonate

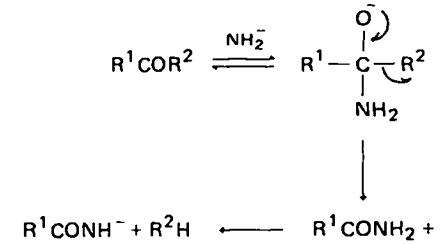
and cyclohexene[1334]. Cyclohexene is converted to cyclohexene oxide during the reaction.

Carboxamides can be prepared by the reaction of nitriles with formic acid and hydrogen chloride or hydrogen bromide[1335]. This efficient method gives excellent yields of amides from aliphatic, aromatic and unsaturated nitriles.

Nitriles are converted to amides under essentially neutral conditions upon refluxing with manganese dioxide in aqueous dioxane[1336]. Palladium chloride-catalysed hydrolysis of nitriles also takes place without added acid or base[1337]. Two other mild methods for effecting hydrolytic production of amides under neutral conditions involve the use of chloropentammineruthenium(III) chloride, $[(NH_3)_5RuCl]Cl_2$[1338] or homogeneous tertiary phosphine–metal–hydroxy complexes such as *trans*-$Rh(OH)(CO)(PPh_3)_2$[1339].

2. *Cleavage of ketones*

Non-enolizable ketones undergo cleavage with sodium amide to form carboxamides and a hydrocarbon residue. This rather general process, known as the Haller–Bauer reaction[1340], occurs by attack of amide ion at the carbonyl carbon, followed by decomposition of the adduct into a hydrocarbon anion and an amide (equation 558). If R^2 is more electron-attracting than R^1 the cleavage will occur in

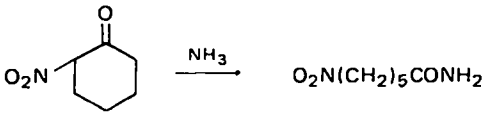


(558)

the manner shown in the accompanying scheme. The Haller–Bauer reaction is one of the few methods which is satisfactory for the synthesis of amides possessing a quaternary α-carbon.

The recent finding that commercial sodium amide can be used for ketone cleavage if it is activated by equimolar amounts of 1,4-diazabicyclo[2.2.2]octane, simplifies the experimental procedure, which had previously required freshly prepared sodium amide[1341].

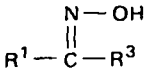
Reaction of 2-nitrocyclohexanone with ammonia results in Haller–Bauer-type cleavage to form ω-nitrocaproamide in 94% yield (equation 559)[1342].



(559)

C. Amides by Rearrangements

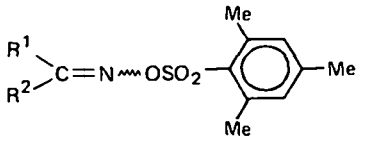
The Beckmann rearrangement[836-838,1343], involves rearrangement of oximes to substituted amides under the influence of phosphorus pentachloride, concentrated sulphuric acid or various other reagents (equation 560). The group *trans* to the hydroxy group is usually the one which migrates.



(560)

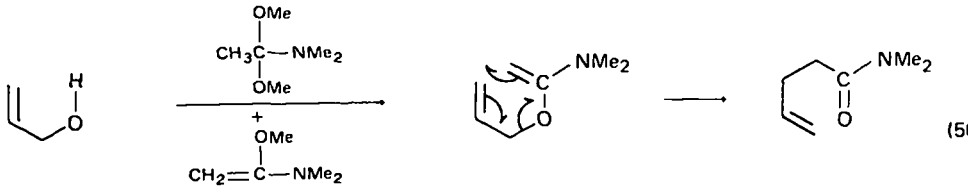
Among the new reagents which have been shown to catalyse Beckmann rearrangements, triphenylphosphine in carbon tetrachloride effects the conversion of various alkanone oximes to amides in good yields under mild, neutral conditions[1344]. Aldoximes are isomerized to unsubstituted amides by means of silica gel in refluxing xylene[1345]. This procedure is claimed to be superior to other known methods of aldoxime rearrangement. Ketoximes have been found to undergo rearrangement in HMPA at 225–240°C to afford the appropriate amides in good yields[1346]. *N,N*-Dimethyldichloromethaniminium chloride effects rearrangement of ketoximes to amides, while aldoximes are converted to nitriles with this reagent[1347].

Reaction of ketones with *O*-mesitylenesulphonylhydroxylamine affords *O*-mesitylenesulphonyloximes, which in turn undergo facile rearrangement to form carboxamides on treatment with basic alumina in methanol (equation 561)[1348].



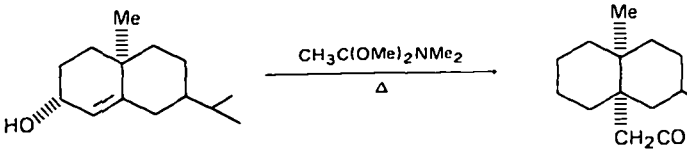
(561)

In 1964, Eschenmoser and coworkers reported a novel Claisen-type rearrangment which results in transformation of allylic alcohols into γ,β-unsaturated amides (equation 562)[1349]. These reactions are accomplished by heating the appropriate

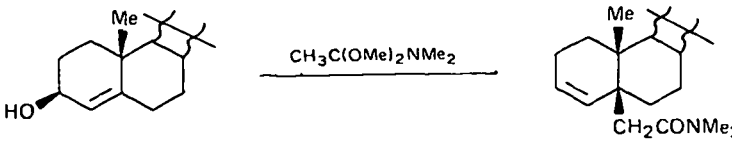


(562)

alcohol with a mixture of *N,N*-dimethylacetamide dimethyl acetal and 1-dimethylamino-1-methoxyethylene in xylene. Formation of the unsaturated amide occurs via a [3,3]-sigmatropic rearrangement of the ketene *N,O*-acetal formed from the allylic alcohol. The overall result is a shift of the alcohol double bond to the site of the original hydroxyl group and transfer of the CH_2CONMe_2 group to the terminal site of the original allylic system. The stereospecific nature of these reactions is illustrated by equations (563) and (564).

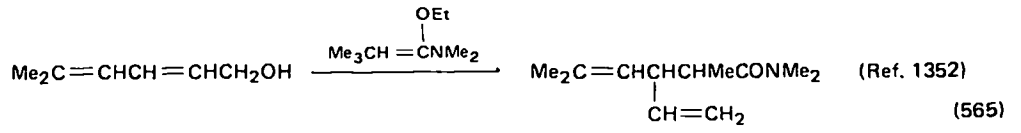


(Ref. 1350) (563)

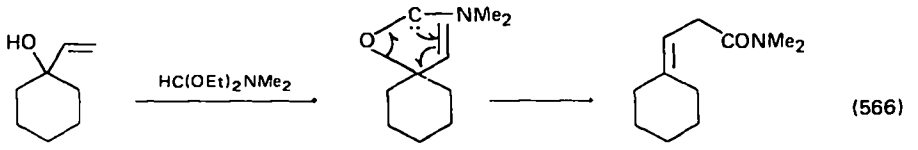


(Ref. 1351) (564)

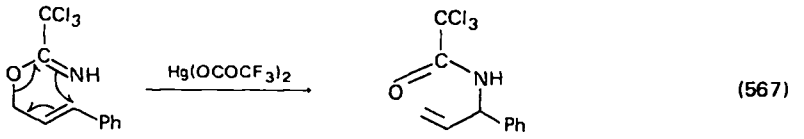
Reactions of allylic alcohols with 1-dimethylamino-1-methoxypropylene-[1352,1353] and 1-dimethylamino-1-ethoxypropylene[1354] lead to introduction of an α-substituted *N,N*-dimethylpropionamide residue at the terminus of the allylic system (equation 565). Recently, it has been found that allylic alcohols can be



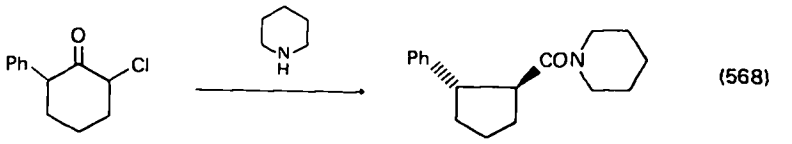
transformed into homologous amides by *N,N*-dimethylformamide acetals (equation 566)[1355]. These reactions, which lead to transfer of a one-carbon amide residue,



are assumed to proceed via [2,3]-sigmatropic rearrangement of an intermediate carbene. Allylic trichloroacetimidates, which are conveniently prepared from allylic alcohols and trichloroacetonitrile, undergo both thermal and mercuric ion-catalysed [3,3]-sigmatropic rearrangements to form *N*-allyl trichloroacetamides (equation 567)[1356]. Here, nitrogen, rather than carbon, is transferred to the terminal allylic position.



The Favorskii rearrangement[871–873] can serve as a method of amide synthesis in the case of certain α-halo-α'-aryl ketones (equation 568)[1357].

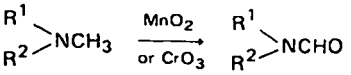


The Willgerodt reaction, which may be considered as a rearrangement process leading to carboxamides, has been reviewed recently[1358].

The Chapman rearrangement, involving thermal isomerization of *N*-aryl and *N*-alkyl imidates to *N,N*-disubstituted amides, has been discussed in detail elsewhere[1359].

D. Amides by Oxidation

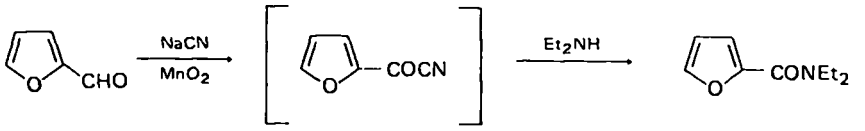
N,N-Dialkylformamides are produced upon treatment of *N*-methyl tertiary amines with oxidizing agents such as manganese dioxide[1360] or chromic anhydride (equation 569)[1361]. Similar oxidations have been accomplished with molecular oxygen in the presence of a platinum catalyst[1362]. Interestingly, *N*-demethylation



(569)

rather than oxidation occurs when platinum-catalysed aerations are carried out in aqueous solutions[1363].

Oxidation of aromatic and α,β-unsaturated aldehydes with manganese dioxide in the presence of sodium cyanide and ammonia or an amine leads to amides (equation 570)[1364]. The mechanism of this reaction appears to involve intermediate formation of an acyl cyanide.



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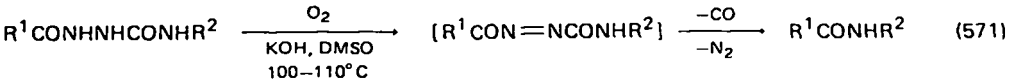
Treatment of 1-acylsemicarbazides with oxygen produces amides in moderate to good yields (equation 571)[1365]. The reaction is assumed to proceed through a diacyldiazene intermediate, which loses carbon monoxide and nitrogen.



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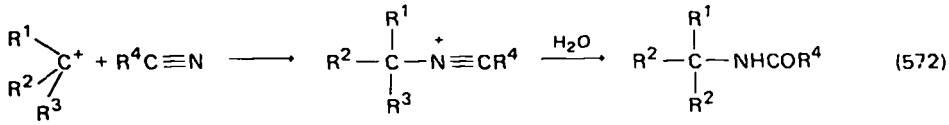
E. Amides by Acylamination

Reactions in which an acylamino (—NHCOR) function is introduced directly into an appropriate substrate are classified as acylaminations.

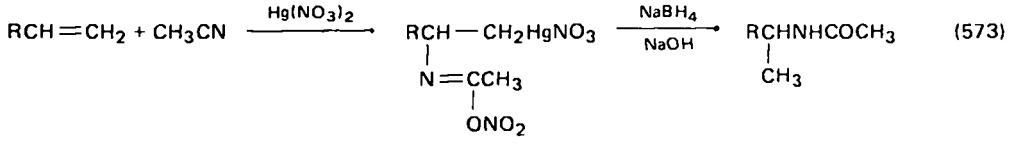
The Ritter reaction[1366] constitutes the most versatile method for the synthesis of amides by acylamination (equation 572). This reaction involves addition of a



(572)

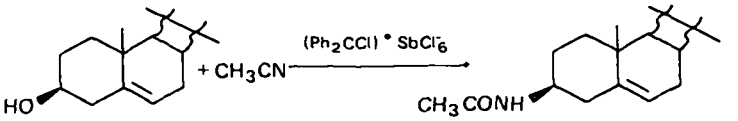
nitrile to a carbonium ion in the presence of sulphuric acid to form a nitrilium salt. Subsequent dilution of the reaction mixture with water affords an *N*-substituted amide.

A number of recent applications of the Ritter reaction have involved new methods for the generation of carbonium ions necessary for combination with the nitrile component of the reaction. With olefinic substrates, hydrogen fluoride is claimed to be superior to sulphuric acid[1367]. Treatment of cyclic or terminal olefins with mercury(II) nitrate in acetonitrile and subsequent reduction of the intermediate organomercury compounds with sodium borohydride provides a convenient method for acylamination of olefins (equation 573)[1368].



(573)

Although the Ritter reaction works with benzylic alcohols[1369], primary aliphatic carbinols do not react satisfactorily. This limitation can be circumvented by treatment of primary alcohols such as *n*-decanol with the hexachloroantimonate salts of chlorodiphenylmethylium, dichlorophenylmethylium or pentachloroallylium cations in nitrile solvents[1370]. These cationic reagents can also be employed to convert cholesterol to 3-β-acetamidocholest-5-ene (equation 574), a transformation that does not proceed under simple Ritter conditions.



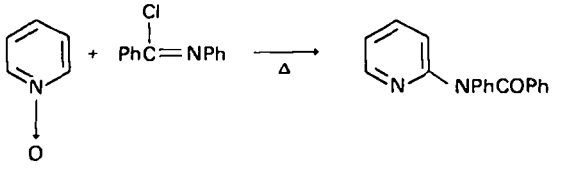
(574)

Cyanohydrins participate in the Ritter reaction with *t*-butyl alcohol to afford *N*-*t*-butyl α-hydroxy amides (equation 575)[1371]. Oxidation of the α-hydroxy

$$RCH(OH)CN \xrightarrow[H_2SO_4]{t\text{-}BuOH} RCH(OH)CONHBu\text{-}t \xrightarrow[2.\ H_3O^+]{1.\ CrO_3} RCOCOOH \qquad (575)$$

amides followed by acid hydrolysis leads to α-keto acids. Anodic oxidations of alkyl iodides[1372] and alkanoic esters[1373] in the acetonitrile solution produce *N*-substituted acetamides. These reactions appear to take place through a carbonium-ion mechanism analogous to the Ritter reaction. Tertiary alkyl bromides react with nitriles to form amides in a modification of the Ritter reaction which does not require an internal catalyst[1374].

Direct acylamination of pyrindine *N*-oxides with an imidoyl chloride can be carried out by heating the reactants in ethylene chloride (equation 576)[1375].



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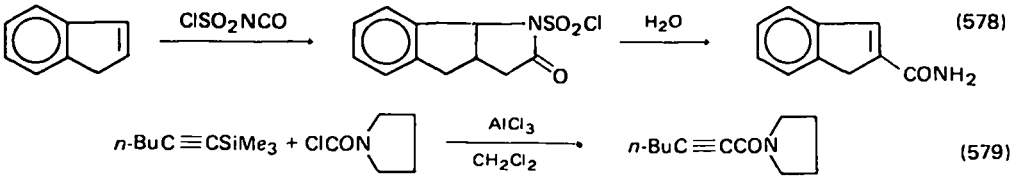
F. Amides by Carboxamidation

A number of methods for electrophilic aromatic carboxamidations have been reviewed[1376,1377]. Recently, direct carboxamidation of aromatic substrates has been achieved in modest yields with urea in the presence of excess aluminium chloride (equation 577)[1377]. 2-Indenecarboxamide has been synthesized in good

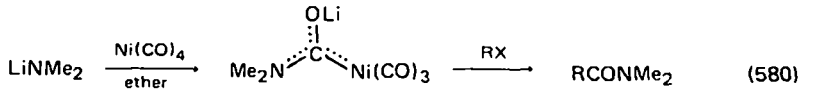
$$ArH + H_2NCONH_2 \xrightarrow{AlCl_3} ArCONH_2 \qquad (577)$$

yield by hydrolysis of the intermediate lactam formed by treatment of indene with chlorosulphonyl isocyanate (equation 578)[1378]. This procedure represents a potentially general method for carboxamidation of unsaturated substrates.

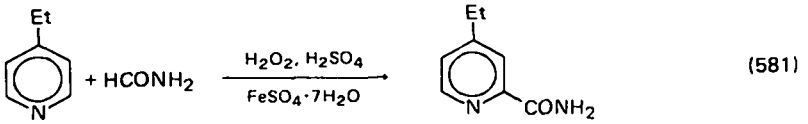
α,β-Acetylenic carboxamides can be conveniently prepared by reacting α-trimethylsilylalkynes with aminocarbonyl chlorides in the presence of a molar equivalent of aluminium chloride (equation 579)[1379].



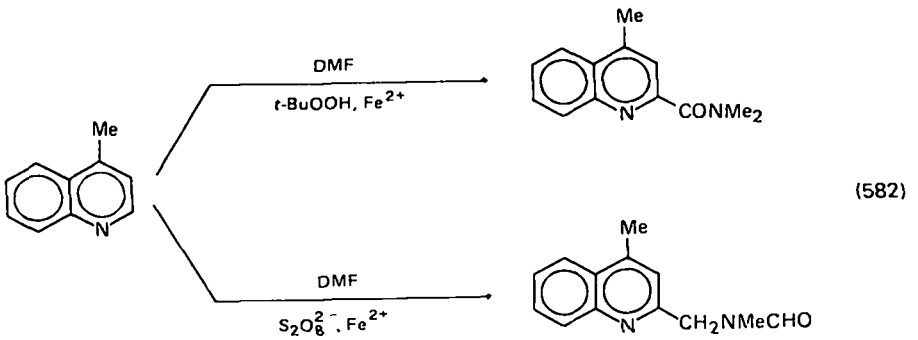
Nucleophilic carboxamidation of alkyl, aryl, vinyl and acyl halides can be accomplished in good yields with lithium dimethylcarbamoylnickel tricarbonylate, which is prepared from lithium dimethylamide and nickel tetracarbonyl in ether (equation 580)[1380].



Free-radical carboxamidation of heteroaromatic bases has been accomplished by reaction of the carbamoyl (•$CONH_2$) radical, formed by hydrogen abstraction from formamide, with the protonated form of various heteroaromatics including pyridine, quinoline, isoquinoline, pyrazine, quinoxaline, benzothiazole and benzimidazole (e.g. equation 581)[1381,1382]. Substitution takes place selectively at the most



electrophilic positions of the heterocyclic substrate. When DMF is allowed to react with quinoline in the presence of certain oxidizing agents, the reaction is complicated by formation of two radicals from the DMF molecule. However this difficulty can be overcome by varying the nature of the oxidant[1382,1383]. For example, lepidine yields mainly the 2-carboxamide upon treatment with DMF in the presence of *t*-butylhydroperoxide and ferrous ion, while substitution at a methyl group of DMF occurs when peroxidisulphate is employed as the oxidizing reagent (equation 582).



Photochemical reactions of formamide with benzene and alkylbenzenes in the presence of acetone, benzophenone or acetophenone as photoinitiators lead to

carboxamidation of the ring and side chains, respectively[1384]. Thus, benzene gives benzamide and toluene is converted mainly to phenylacetamide along with some *o*-toluamide. This method suffers from the disadvantage that yields rarely exceed 30%.

Halogenation or oxidation of the alkyl or acyl complexes derived from sodium tetracarbonylferrate(−II)[257] in the presence of amines affords amides via a process which may be regarded as carboxamidation of alkyl halides or tosylates (equation 583). Aryl, heterocyclic and vinylic halides undergo carboxamidation upon reaction

$$n\text{-}C_5H_{11}Br \xrightarrow[2.\ I_2,\ Et_2NH]{1.\ Na_2Fe(CO)_4,\ CO} n\text{-}C_5H_{11}CONEt_2 \qquad (583)$$

with carbon monoxide and primary and secondary amines in the presence of a dihalobistriphenylphosphinepalladium(II) catalyst[1385]. The stereospecificity of this reaction is demonstrated in equation (584).

$$\begin{matrix} H \\ Ph \end{matrix}\!\!>\!C\!=\!C\!<\!\!\begin{matrix} Br \\ H \end{matrix} + CO + PhNH_2 \xrightarrow[60°C,\ 1\ atm]{PdBr_2Ph_3} \begin{matrix} H \\ Ph \end{matrix}\!\!>\!C\!=\!C\!<\!\!\begin{matrix} CONHPh \\ H \end{matrix} \qquad (584)$$

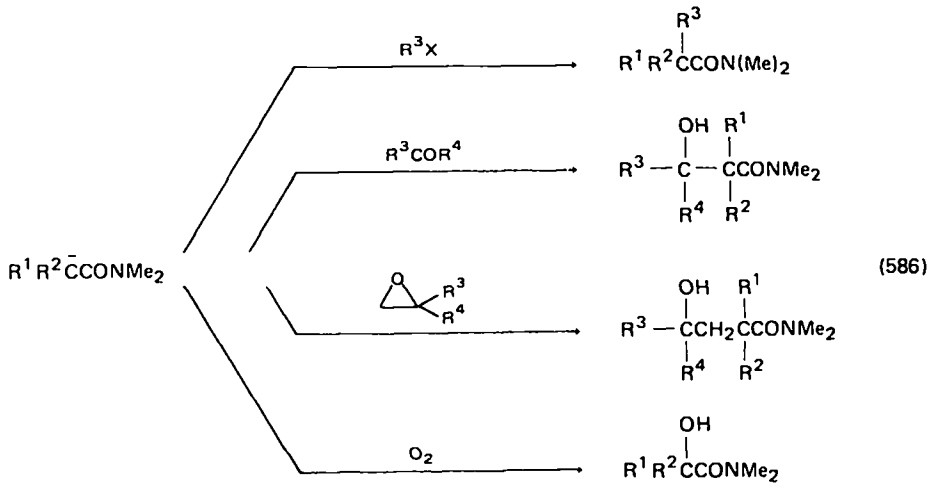
Related carboxamidations have been performed on alkyl and vinyl halides using nickel tetracarbonyl and secondary amines in the presence of alkoxide bases[252,253].

G. Amides by Condensation Reactions

Several new procedures for amide synthesis involve condensations of electrophilic reagents with α-carbanions derived from amides. These reactions, which bear a strong resemblance to active hydrogen condensations involving esters, can be used for the synthesis of various elaborated amides from readily available precursors.

Generation of α-carbanions from *N,N*-dialkylcarboxamides can be effected by means of sodium amide[1386–1389], *n*-butyllithium[1390] or LDA (equation 585)[1391,1392]. The resulting α-anions react with alkyl

$$R^1\text{—}\underset{R^2}{\underset{|}{C}}HCONMe_2 \xrightarrow{B^-} R^1\text{—}\underset{R^2}{\underset{|}{\overset{-}{C}}}CONMe_2 \qquad (585)$$



(586)

halides[1386-1388,1390,1391], aldehydes and ketones[1390], epoxides[1389] and molecular oxygen[1392] to afford α-alkyl, β-hydroxy, γ-hydroxy and α-hydroxy amides, respectively (equation 586).

Zinc derivatives analogous to Reformatsky reagents can be prepared from α-bromo-*N*,*N*-dialkylamides[1393].

Reaction of *N*-alkylacetamides with two equivalents of *n*-butyllithium produces 1,3-dianions, which react with aryl aldehydes to produce *N*-alkyl-β-hydroxy amides[1394].

$$CH_3CONHR^1 \xrightarrow{2\,n\text{-BuLi}} \bar{C}H_2CO\bar{N}R^1 \xrightarrow{R^2CHO} R^2CH(OH)CH_2CONHR^1 \quad (587)$$

Reactions of aldehydes and ketones with DMF in THF–ether in the presence of LDA at −78°C produces α-hydroxy-*N*,*N*-dimethylamides (equation 588)[1395].

$$\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}O + HCONMe_2 \xrightarrow{LDA} R^1{-}\overset{OH}{\overset{|}{C}}CONMe_2 \quad (588)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R^2$$

Metalated *N*-phenyl phenylketenimines react with benzaldehyde or α,β-unsaturated aldehydes in a Wittig-type process to yield α-phenylacrylanilides (equation 589)[1396].

$$RCHO + Ph{-}\overset{M^+}{\overset{|}{\bar{C}}}{=}C{=}NPh \longrightarrow PhC{=}\overset{M^+}{\overset{|}{C}}{-}\bar{N}Ph$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R{-}CH{-}O$$

$$\xrightarrow{H_3O^+} RCH{=}\overset{Ph}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NHPh \quad (589)$$

Metalation of α,β-ynamines by alkylithium–TMEDA complexes leads to formation of lithium derivatives which undergo terminal alkylation on treatment with alkyl halides. Subsequent hydrolysis or alcoholysis of the elaborated ynamines affords amides or esters, respectively (equation 590)[1397].

$$CH_3C{\equiv}C{-}N \xrightarrow[TMEDA]{t\text{-BuLi}} LiCH_2C{\equiv}C{-}N \xrightarrow{RX} RCH_2C{\equiv}C{-}N \quad (590)$$

$$RCH_2C{\equiv}C{-}N \xrightarrow[Et_2O]{alumina} RCH_2CH_2CON$$

H. Amides by Miscellaneous Methods

Formamides can be prepared by carbonylation of primary[1398] and secondary amines[1399,1400] using ruthenium[1398,1400] and copper[1399] catalysts (equation

591). Formylation of secondary amines has also been accomplished by reaction with carbon dioxide and hydrogen[1401], and by treatment of the amine with chloroform and aqueous sodium hydroxide in the presence of a phase-transfer catalyst such as triethylbenzylammonium chloride[1402]. The latter reaction involves attack of dichlorocarbene at the amine nitrogen.

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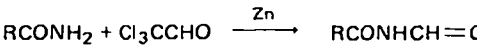
N,β,β-Dichlorovinylamides have been prepared recently by reaction of chloral with amides in the presence of powdered zinc (equation 592)[1403].



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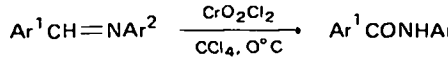
Treatment of *N*-phenylimines with chromyl chloride affords anilides in good yields (equation 593)[1404]. The reaction presumably involves formation of intermediate oxaziranes, which isomerize to the observed amides.



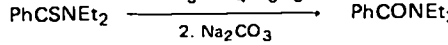
(593)

Reductive hydrolysis of azlactones in alcoholic ammonia at room temperature leads to α-benzoylamino acid amides (equation 594)[1405]. This procedure is more

(594)

convenient than earlier methods which require hydrolysis of the azlactone to the unsaturated acylamino acid followed by a hydrogenation step.

A general method for conversion of *N*,*N*-dialkylthioamides to *N*,*N*-dialkylcarboxamides involved treatment of the thioamide with trimethyloxonium fluoroborate in dry benzene, and then hydrolysis with aqueous sodium carbonate (equation 595)[1406].



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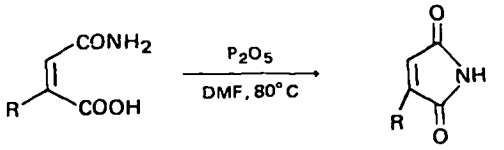
VII. SYNTHESIS OF IMIDES

Several recent reviews provide detailed coverage of general methods for the synthesis of imides[1407-1409]. In light of this, we have chosen to outline several procedures which have appeared since these articles were written.

A. Imides by Acylation Reactions

Acylations of amines and amides with acyl halides or anhydrides constitute a general method for the preparation of imides. For example, the synthesis of various

cyclic imides can be accomplished by treatment of cyclic anhydrides with ammonia or an amine to form an amic acid, which is then cyclized thermally or in the presence of a suitable dehydrating agent. In connection with the synthesis of the *C*-nucleoside, showdomycin, phosphorus pentoxide suspended in DMF has been demonstrated to be a mild and potentially general reagent for cyclization of α-substituted maleamic acids where other procedures fail (equation 596)[1410].



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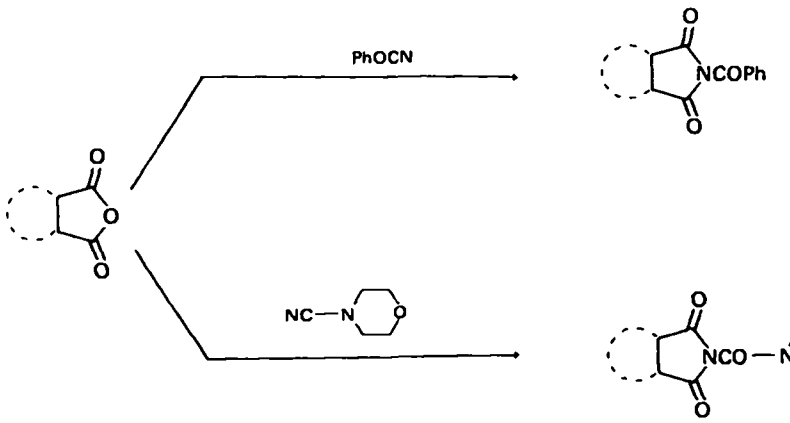
Cyclic anhydrides of aromatic and cycloaliphatic dicarboxylic acids react with cyanates and cyanamides to form *N*-acylated imides (equation 597)[1411].



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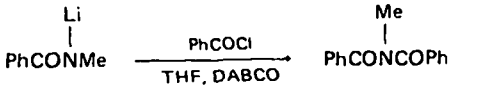
Acylation of mono- and di-*N*-lithio salts of amides has been accomplished with aroyl chlorides in the presence of Lewis bases such as 1,4-diazabicyclo-[2.2.2]octane (DABCO) (equation 598). In the absence of DABCO, which in-



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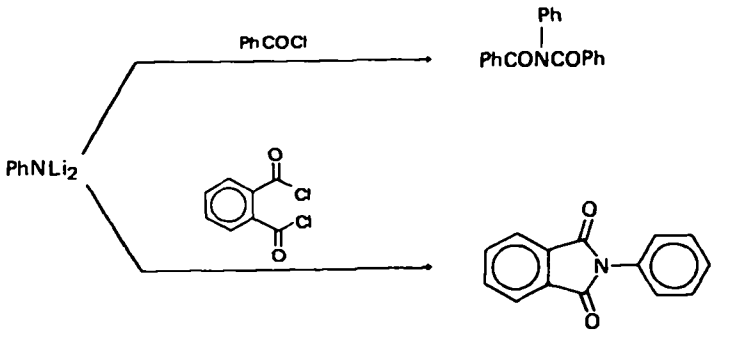

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creases the rate of acylation through coordination with the lithium cation, yields of imides drop sharply[1412]. The *N,N*-dilithio salts of aniline and benzamide react with aroyl chlorides in the presence of DABCO to form dibenzamides and tribenzamides, respectively (equations 599 and 600). Dilithioaniline also condenses with phthaloyl

$$PhCONLi_2 \xrightarrow{PhCOCl} (PhCO)_3N \qquad (600)$$

chloride to produce *N*-phenylphthalimide. These acylation procedures offer considerable promise as a general approach to imide synthesis, with the possible limitation that aliphatic acyl halides may be unsatisfactory because of the strongly basic character of the lithio salts employed. Acylation of primary amides with aliphatic chlorides in methylene chloride in the presence of pyridine, 2-methylpyridine or 2,6-dimethylpyridine leads directly to triacylamides rather than simple imides (equation 601)[1413].

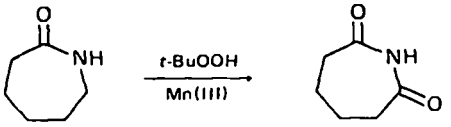
$$2\ RCOCl + RCONH_2 \xrightarrow[-20\ to\ 40°C]{CH_2Cl_2} (RCO)_3N \qquad (601)$$

Reaction of cyclic imino esters with acyl chloride produces *N*-acyllactams (equation 602)[1414]. This procedure would appear to be applicable to acyclic imino esters also.

(602)

B. Imides by Oxidation Reactions

Oxidation of lactams and *N*-alkylamides to imides has now been developed into a useful synthetic method[1415]. Excellent results are obtained with lactams by using a hydroperoxide or peroxy acid in the presence of manganese(II) or manganese(III) acetylacetonates. This mild oxidative procedure represents the first convenient method for synthesizing several relatively inaccessible imides such as adipimide. Acylic *N*-alkylamides are oxidized to linear imides more satisfactorily with peroxyacetic acid than with hydroperoxide oxidants.



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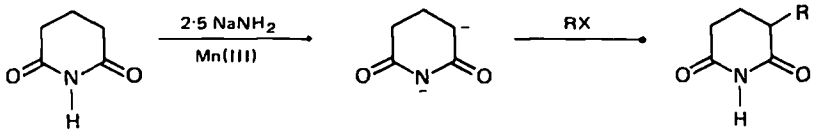
C. Imides by C- and N-Alkylations

Elaboration of preformed imides can be effected by abstraction of the NH proton as well as an α-hydrogen to form a dianion intermediate such as that derived from glutarimide[1416]. Subsequent alkylation of the dianion occurs exclusively at the more nucleophilic carbanion site to produce 2-alkyl glutarimides (equation 604). Aldehydes and ketones react with the glutarimide dianion to afford 2-(α-hydroxy)alkylglutarimides, while reactions with aromatic esters produce 2-aroylglutarimides. Similar dianion approaches have been used to prepare substituted

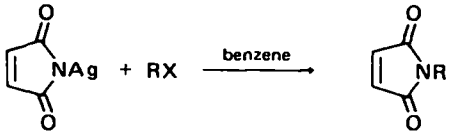


(604)

2,4-morpholinediones[1416], 2,4-thiomorpholinediones[1416] and 2,4-thiazolidinediones[1417]. Phenylacetylureas can be converted to trianions, which undergo regiospecific alkylations at the benzylic position (equation 605)[1418].

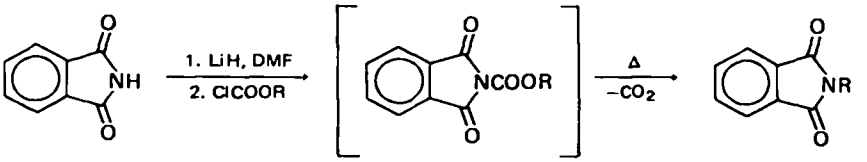
$$PhCH_2CONHCONHR^1 \xrightarrow[NH_3]{4\cdot5\ KNH_2} Ph\bar{C}HCO\bar{N}CO\bar{N}R^1 \xrightarrow{R^2X} PhCHR^2CONHCONHR^1 \quad (605)$$

Preparation of *N*-alkylimides can often be realized by one or more of the classical acylation reactions described above. However, certain *N*-alkylamic acids are cyclized with difficulty, and *N*-alkylation of the unsubstituted cyclic imide becomes the preferred method of synthesis. Preparation of *N*-alkylmaleimides, which are often available in low yields by cyclization of *N*-alkylmaleamic acids, is smoothly effected by coupling of alkyl or aralkyl halides with the silver salt of maleimide (equation 606)[1419]. Another convenient procedure for *N*-alkylation of



(606)

imides consists of initial conversion of the imide to the lithio salt by means of lithium hydride in DMF, followed by addition of a chloroformate ester to the reaction mixture at 60–100°C[1420]. The intermediate *N*-carboethoxyimide undergoes decarboxylation at this temperature to afford the desired *N*-alkylimide (equation 607).



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VIII. ACKNOWLEDGMENTS

We are delighted to acknowledge the contributions of our typists, Mrs. Brenda Mills and Mrs. Mary Jane Altizer. Mrs. Mills, who typed most of the manuscript, also provided all structural drawings. Miss Susan Stevens did a monumental job in organizing and checking the more than 4000 primary references collected for this review. Without the help of these dedicated and pleasant ladies our task would have been impossible. We are also grateful to the Department of Chemistry for providing facilities and financial support and to the National Aeronautics and Space Administration (Grants NSG-1064 and NSG-1286) and the National Science Foundation (Grant CHE 74-20520) for support of our research programmes during the writing of this chapter.

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER 8

The chemistry of lactones and lactams

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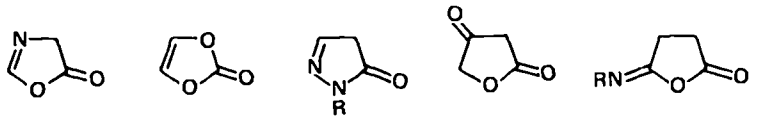
I. INTRODUCTION

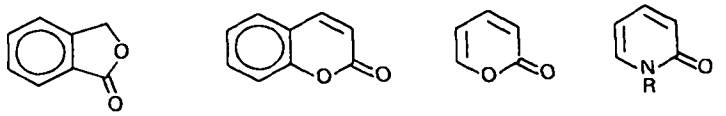
Lactones (1) and lactams (2) are internal esters and amides of hydroxy and aminocarboxylic acids, respectively. Ring systems of all possible sizes and various degrees of unsaturation will be described but because of the vastness of the subject

(1) (2)

some restrictions had to be imposed. Thus, lactones and lactams containing additional heteroatoms in the ring, such as oxazolinones (3), vinylene carbonate (4) and pyrazolinones (5) are omitted, as are compounds with exocyclic double bonds attached to heteroatoms, e.g. tetronic acids, the enol tautomers of β-oxo-γ-lactones (6) and isoimides (7). Futher, bi- and polycyclic systems are only rarely mentioned; hence phthalides, e.g. meconin (8), the first lactone to be isolated, and coumarin (9) and its derivatives are not dealt with. A problem arose concerning fully conjugated systems, such as 2-pyrones (10) and 2-pyridones (11). It was decided to include the former but to exclude the latter, because 2-pyrones behave as unsaturated lactones, whereas the chemistry of the pyridones is dominated by their close relationship to the aromatic pyridine structure.



(3) (4) (5) (6) (7)

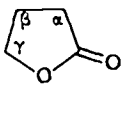


(8) (9) (10) (11)

Review articles are cited where possible; other references are, in general, to recent papers containing leading references to earlier work. It follows that in many instances the discoverer of a reaction or of a class of compounds is not given the credit due to him.

Since lactones and lactams are heterocyclic compounds, they should, strictly speaking, be named as such, as in recent issues of *Chemical Abstracts*. However, it is customary to avoid the resulting cumbersome nomenclature and to name the compounds after the parent hydroxy or amino acid and this convenient practice will be followed. Thus lactone 12 is referred to as a γ-lactone rather than as a derivative of furan, because it is the cyclic ester of γ-hydroxybutyric acid, and lactam 13 is ε-caprolactam. The Greek prefix, then, indicates the ring size, α, β, , δ . . . signifying rings of 3, 4, 5, 6 . . . atoms. In another system of nomenclature, which will occasionally be used here, lactones are referred to as 'olides', e.g. 12 is named 'butanolide'. It is important to realize that a compound such as nonalide

possesses a ten-membered ring, since 'nona' refers to the number of cyclic carbon atoms.



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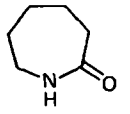

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II. LACTONES[1]

γ-Butyrolactone was first obtained by Saytzeff in 1874[2], who regarded it as succindialdehyde. Fittig and his students, in a long series of publications, established the relationship between lactones and hydroxy and olefinic acids[3]. Lactones, particularly γ-lactones, occur widely distributed in nature[4] as simple butenolides, sesquiterpene butenolides, cardenolides (steroidal butenolides), butadienolides and antibiotic macrolides. The bouquet of wines is largely due to trace amounts of γ-butyrolactone and its derivatives[5].

In general, 5-membered ring lactones are the most easily formed and the most stable. This is shown *inter alia* by their formation from sugar acids bearing hydroxyl groups in the α-, β-, γ-, δ- and ε-positions and by the isomerization of δ- to γ-lactones[6].

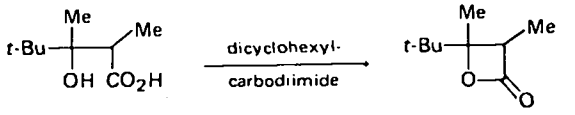
A. General Methods of Synthesis

Lactones of all ring sizes are generally formed from hydroxy carboxylic acids or their synthetic equivalents, such as halogen-substituted acids and olefinic acids. The ease of lactonization depends largely on ring size, γ-lactones being formed most readily because of the ease with which the reacting centres can be brought into proximity. This is nicely illustrated by the relative rates of alkaline hydrolysis of five bromocarboxylic acids, which proceeds largely via intermediate lactones (Table 1)[7].

TABLE 1. Rates of alkaline hydrolysis

Acid	Rate (10^5 k/min)
α-Bromohexanoic	3.3
β-Bromohexanoic	210
γ-Bromopentanoic	33,000
ε-Bromohexanoic	10
ζ-Bromoheptanoic	2.6

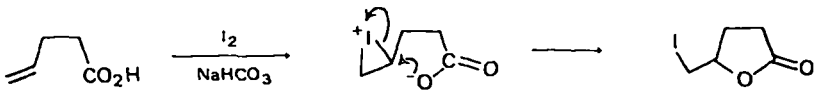
The lactonization of hydroxy carboxylic acids in the presence of mineral acids or on heating can, in general, only be applied to the preparation of γ- and δ-lactones. β-Hydroxy acids cyclize only in special cases when there is relief from steric compression, e.g. equation (1)[8]. γ-Lactones are produced from α, -, β,γ-, and



(1)

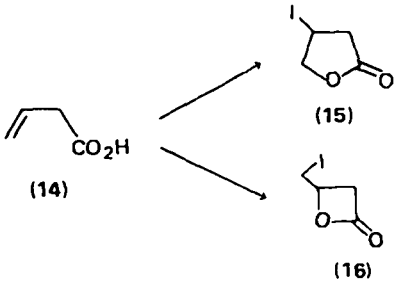
γ,δ-olefinic acids on distillation or in the presence of inorganic acids; in the case of α,β-unsaturated acids, rearrangement to the β,γ-unsaturated acids precedes lactonization[9].

A related synthesis is the formation of iodolactones from olefinic acids by the action of iodine and aqueous alkali, the 'halolactonization reaction' (equation 2)[10-12]. β,γ-Unsaturated acids usually yield β-iodo-γ-lactones, e.g.

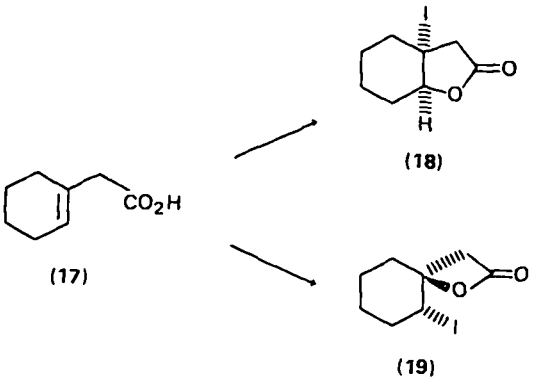


(2)

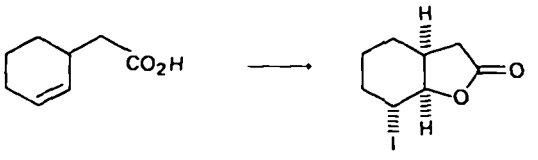
14 → **15** and **17** → **18**, but if a two-phase system is employed, in which the lactone is extracted as it is formed, γ-halogeno-β-lactones, such as **16**, are isolated; the β-lactones are the products of kinetic control and are converted into γ-lactones under the usual iodolactonization conditions[13].



γ-Iodo-β-lactones are also obtained when thallium (I) salts of β,γ-unsaturated acids are treated with iodine; thus acid **17** affords a mixture of the lactones **18** and



19[14]. In the case of γ,δ-olefinic acids, δ-iodo-γ-lactones, e.g. **20** → **21**, are formed in preference to δ-lactones unless the γ-lactone is highly strained.



The iodolactonization reaction has played an important part in the assignment of configuration to Diels–Alder adducts; thus, only the *endo* isomer of the maleic acid–cyclopentadiene adducts is capable of yielding an iodolactone (equation 3). Halolactonization of the amides formed from α,β-unsaturated acids and (*S*)-proline proceeds almost stereospecifically; successive dehalogenation and hydrolysis of the lactones give optically active (*R*)-α-hydroxy acids of high optical purity[15].

(3)

Other general methods for preparing lactones are cycloaddition reactions, reduction of cyclic anhydrides of dibasic acids, and ring-expansion of cyclic ketones by means of the Bayer–Villiger oxidation, which is particularly useful for the synthesis of medium and large lactones. These reactions are discussed in detail under the various classes of lactones.

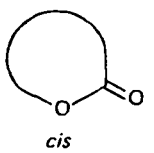
B. General Physical Properties

The infrared spectra of lactones exhibit carbonyl stretching bands which are characteristic of ring size; typical values are as follows:

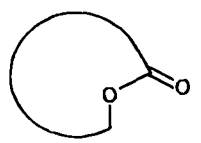
α-Lactones	1895 cm^{-1}
β-Lactones	1840–1810 cm^{-1}
γ-Lactones	1795–1760 cm^{-1}
δ-Lactones	1750–1735 cm^{-1}
ε-Lactones	ca. 1740 cm^{-1}

For higher lactones the values converge to 1740–1730 cm^{-1}, the frequencies observed for aliphatic esters.

The dipole moments of simple lactones of ring size from 4 to 16 were determined by Huisgen and Ott[16]. The moments of the first members of the series up to heptanolide range from 3.7 to 4.4 D, those of the larger from 1.9–2.2 D. The 8-, 9- and 10-membered lactones occupy an intermediate position; from the 12-membered ring upwards the dipole moments remain constant and equal those of open esters. It appears that the changes are due to the transition from the *cis* to the *trans* conformation as the ring size increases; the smaller lactones are in the *cis* conformation, the 8-membered lactone exists as a mixture containing 25% of the *trans* conformer, the 9-membered lactone contains 90–94% of *trans* compound, and the higher lactones from 10 upwards are exclusively *trans*. ORD and CD spectra[17,18] also give information on the configuration of lactones.

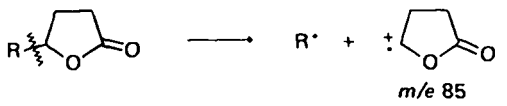


cis



trans

The mass spectra of γ-lactones[19,20] show a fragment of *m/e* 85 due to the fission shown in equation (4). δ-lactones[21] give an analogous fragment of mass 99.

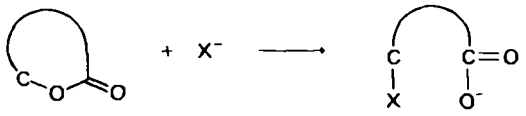


(4)

C. General Chemical Properties

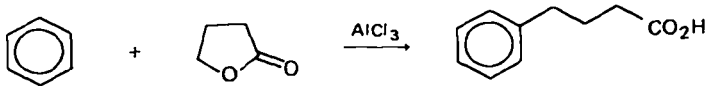
A comparison[16] of the rates of alkaline hydrolysis of 5- to 16-membered lactones supports the conclusions reached on the basis of the dipole-moment studies. The 5- to 8-membered lactones react much faster than the higher lactones because of the *cis* conformation of the former. The larger lactones of ring size 10–16, which, like open esters, have the *trans* structure, hydrolyse at comparable rates; octanolide shows intermediate behaviour. In the series δ-valerolactone > β-propiolactone > γ-butyrolactone > ε-caprolactone the decrease in reactivity is due to the interplay of conformational and angle strain effects[22].

The *cis* conformation of the smaller lactones manifests itself in the ease with which they react with nucleophiles to yield products derived from alkyl-oxygen fission[23] (equation 5). Similarly, γ-lactones alkylate rather than acylate aromatic compounds in the Friedel–Crafts reaction (equation 6). The reactions of lactones with nucleophiles have been studied particularly thoroughly for β-lactones[24] and γ-lactones[25].



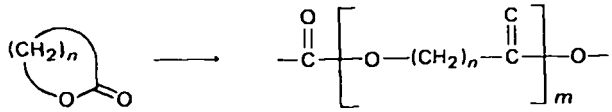
(5)

X = Cl, CN, OR, SR, NO_2, RCO_2 etc.



(6)

A characteristic property of the smaller lactones of ring size 4[26], 6[27], 7[28] and 8[16] is polymerization[29] to give polyesters.

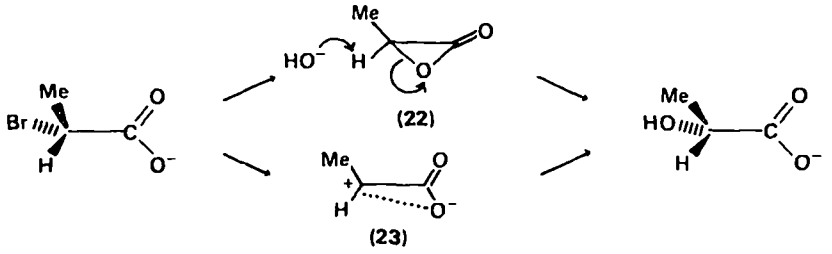


Poly-ε-caprolactone is an important industrial material for the manufacture of polyesters for urethane rubbers, adhesives and coatings.

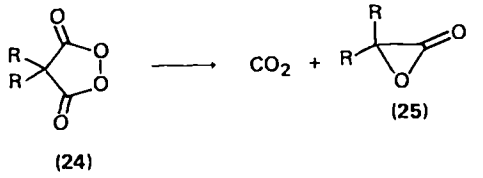
D. α-Lactones

The three-membered lactone system, although often postulated as an intermediate in solvolytic reactions of α-halocarboxylic acids[30], has for many years defied attempts at isolation. Treatment of optically active α-bromopropionic acid with aqueous alkali leads to lactic acid with retention of configuration[31]. The kinetics are of first order, the rate-limiting step being the ionization of bromide[32]. This is consistent with the intermediacy of the α-lactone 22 (or its zwitterionic equivalent 23), which forms lactate anion by alkyl-oxygen fission. INDO calcu-

lations[33] show that the α-lactone structure is much more stable than the semi-open form 23.



The synthesis of α-lactones 25 was eventually achieved[34] by irradiating the peroxides (24, R = Me or *n*-Bu) at 77 K (equation 7); the spiro-α-lactones (26–28) were obtained similarly. Continued irradiation gave ketones, R_2CO and carbon monoxide, while warming to above 100°C led to polyesters.



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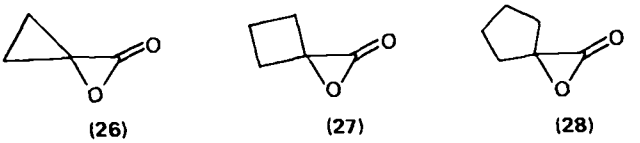
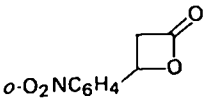


E. β-Lactones[24,35]

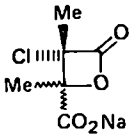
1. Synthesis

In 1883 Einhorn[36] first succeeded in preparing a β-lactone, compound 29, by treating β-bromo-β-(*o*-nitrophenyl)propionic acid with sodium carbonate. In general, salts of optically active β-halocarboxylic acids in an alkaline medium yield β-lactones with inversion of configuration (equation 8).



(8)

The formation of β-lactones in the halolactonization reaction was mentioned in Section II.A; two further examples are (a) the production of stereoisomeric lactones (30) by the action of chlorine on the sodium salts of dimethylmaleic and dimethylfumaric acids[38], and (b) the preparation of the bicyclic lactone 32 from the dihydrobenzoic acid 31[39].



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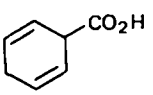

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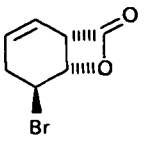

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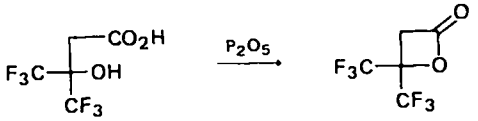
Dehydration of β-hydroxy carboxylic acids cannot be used for making β-lactones as it usually leads to olefinic acids; β-lactones are obtained only in exceptional cases (equations 1 and 9[40]).



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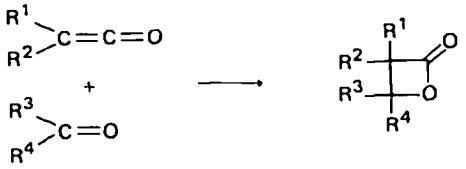
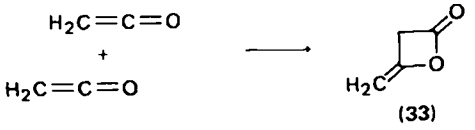
The most general synthesis of β-lactones, the cycloaddition of ketens to carbonyl compounds (equation 10), was discovered by Staudinger[41]. The addition of ketens



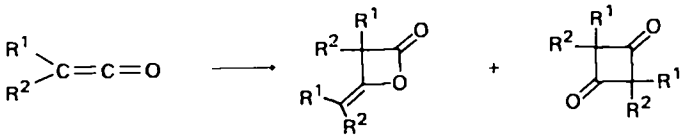
(10)

to ketones usually requires a catalyst except for diphenylketen; zinc salts are particularly effective in the case of aldehydes[42]. The dimerization[43,44] of keten itself to yield diketen (β-methylenepropiolactone) (33) is a special case of this reaction (equation 11). Monoalkylketens (34, R^1 = alkyl, R^2 = H) dimerize in the presence



(33) (11)

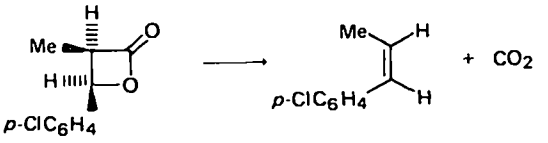
of tertiary amines to give mainly β-lactones (35), but cyclobutan-1,3-diones (36) are also formed[45]. Comparable amounts of lactones and cyclobutanediones are obtained from dialkylketens (34, $R^1 = R^2$ = alkyl)[46].



(34) (35) (36)

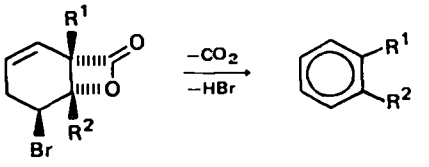
2. Properties

Simple β-lactones give olefins and carbon dioxide on thermolysis. The reaction is concerted or nearly so, since *cis*-β-*p*-chlorophenyl-α-methyl-β-propiolactone (37) gives only the *cis*-arylpropene (38), while the *trans* isomer of 37 gives mainly *trans* olefin[47].



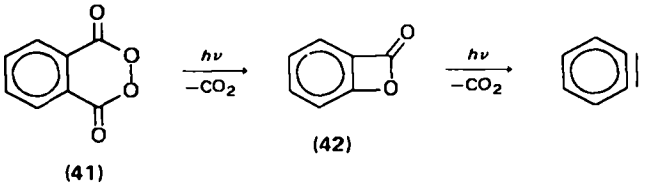
(37) (38)

An interesting application of this fragmentation reaction is the formation of benzene derivatives (40, R^1 = H or Me; R^2 = Me or CH_2OH) by the action of a tertiary amine on the bicyclic lactones 39[48] (cf. Section II.E.1). The synthesis of



(39) (40)

free benzyne was achieved by Chapman and his colleagues[49] by photolysing phthaloyl peroxide (41) in an argon matrix at 8 K; the resulting benzopropiolactone (42) fragmented to benzyne and carbon dioxide on continued irradiation:



(41) (42)

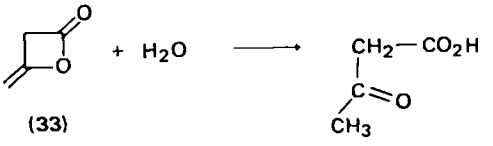
The β-lactone ring is easily opened; even the weakly nucleophilic chloride ion is effective (equation 12)[50]. Hydrolysis of β-lactones to yield β-hydroxy acids pro-

(12)

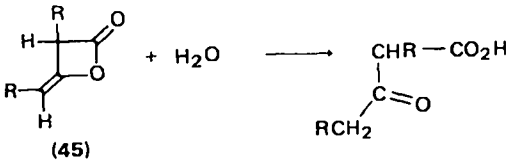
ceeds by alkyl–oxygen fission in pure water, but acyl–oxygen fission occurs under basic or strongly acidic conditions[23,51,52]. Similarly, alcohols, ROH, form ethers (43) under neutral conditions and esters (44) in the presence of acids or bases[53]. With amines, mixtures of products arising from both alkyl-oxygen and acyl-oxygen fission are obtained[35].

(43) (44)

Diketen (33) functions as the inner anhydride of acetoacetic acid (equation 13). The dimers (45) of substituted ketens behave in an analogous fashion (equation 14).

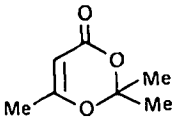


(33) (13)



(45) (14)

Similarly, the action of alcohols and amines on diketen results, respectively, in esters[54] and amides of acetoacetic acid; hydrogen bromide gives acetoacetyl bromide[55]. An adduct (46) is formed from diketen and acetone in the presence of *p*-toluenesulphonic acid[56]. Diketen undergoes a complex reaction with ynamines, $R-C\equiv C-NEt_2$, to yield a mixture of 2- and 4-pyrones (47) and (48)[57].



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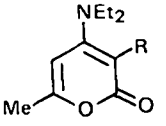

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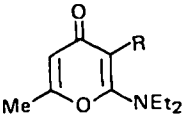
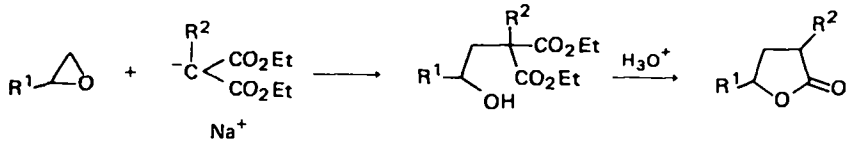


(48)

F. γ-Lactones[1,25]

1. Saturated γ-lactones

The ready formation of γ-lactones from γ-hydroxy, γ-halo-, and unsaturated carboxylic acids has been mentioned in Section II.A. The use of epoxides for the generation of intermediate hydroxy acids is illustrated by equation (15)[58]. The reaction[59] of cyclohexene oxide with metallated isobutyric acid is based on the same principle (equation 16). 2-Oxazolines (49)[60] function as acid equivalents (equation 17).



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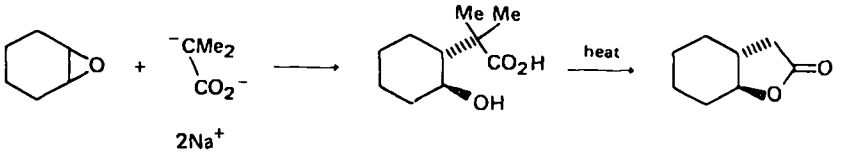

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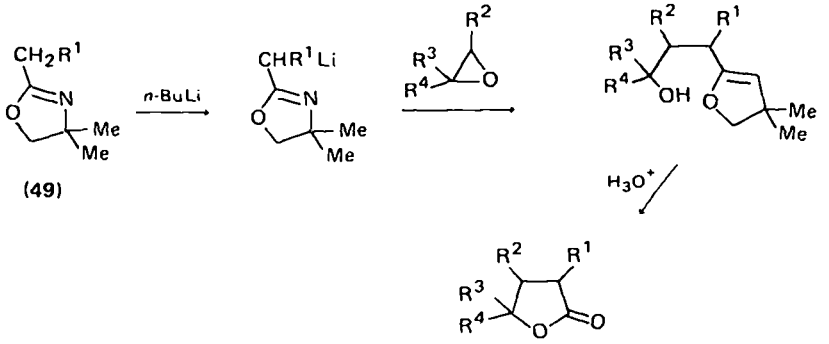
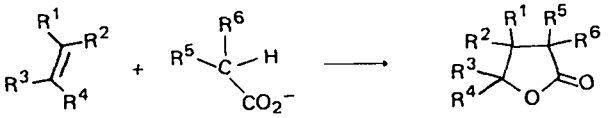


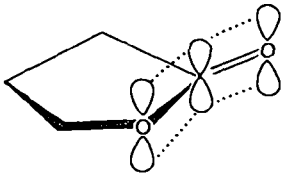
(17)

Olefins react with manganese (III) salts of acetic, propionic, isobutyric and cyanoacetic acids by a free-radical mechanism to afford high yields of γ-lactones (equation 18)[61]; polyunsaturated olefins are preferentially attacked at the terminal double bond. Five-membered cyclic anhydrides, e.g. succinic and phthalic anhydride, are reduced by sodium borohydride to give γ-lactones[62].



(18)

The stability of the γ-lactone system is attributed to the near-planarity of the ring, which allows maximum overlap of the *p*-orbitals (cf. **50**). Substituted γ-lactones may exhibit geometrical isomerism; studies on the base-catalysed equilibration of seven *cis*- and *trans*-γ-lactones (**51**) have indicated that in every case the *cis* isomer is thermodynamically preferred[63].



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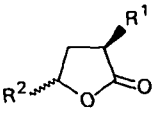
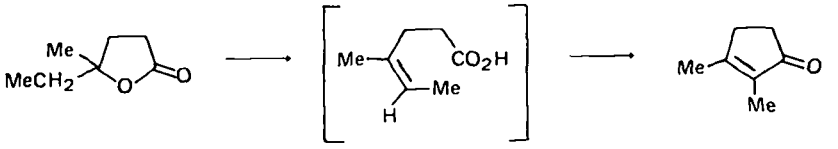


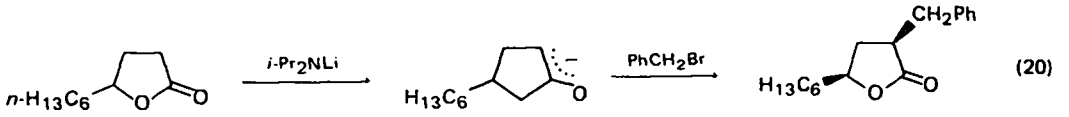
(51)

The action of nucleophilic reagents on γ-lactones has been summarized in Section II.C. Certain substituted γ-lactones form cyclopentenones on treatment with phosphorus pentoxide or polyphosphoric acid[64], presumably by way of unsaturated acids (e.g. equation 19).



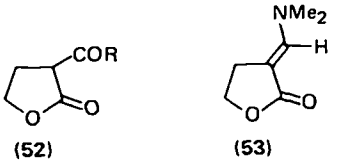
(19)

α-Alkylation of γ-lactones is best carried out via lithium enolates (equation 20)[65]. α-Acyl derivatives (52) are produced by Claisen condensation of γ-lactones



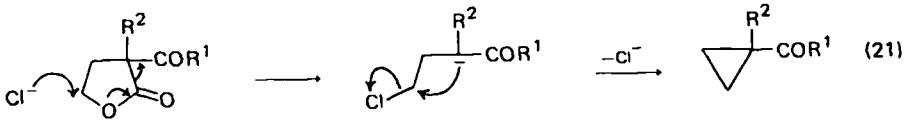
(20)

with carboxylic esters in the presence of sodium ethoxide. Treatment of saturated γ-lactones with tris(dimethylamino)methane, $(Me_2N)_3CH$, yields α-(dimethylaminomethylene) derivatives (53)[66].



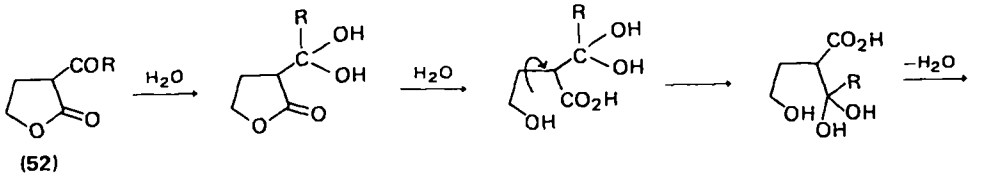
(52) (53)

When α-acyl-γ-lactones are heated with sodium chloride in dimethylsulphoxide, cyclopropanes are produced in good yields[67]. It has been proposed that the reaction involves alkyl-oxygen fission, decarboxylation and cyclization (equation 21).



(21)

α-Acyl-γ-lactones (52) react with aqueous hydrochloric acid to yield tetrahydrofuran-3-carboxylic acids (54) in the 'acyllactone rearrangement'[68]. The products may either lose water to give dihydrofurans (55) or suffer decarboxylation. The reaction has been applied to the synthesis of numerous heterocyclic compounds[69].



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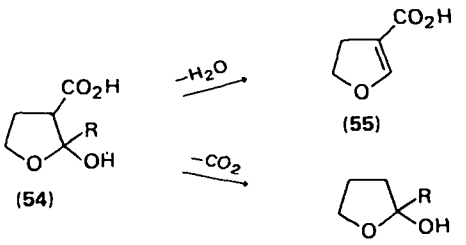
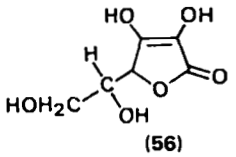


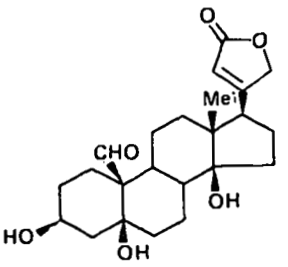
(54) (55)

2. *Unsaturated γ-lactones*

This group comprises lactones with endo- and exocyclic double bonds. The former will be discussed first. Compounds in this class are usually referred to as α,β-

and β,γ-butenolides, the prefix indicating the position of the double bond. Many natural products contain the α,β-butenolide system[4], e.g. ascorbic acid (vitamin C) (56) and the cardiac glycosides[70], which consist of a sugar residue attached to a steroidal aglycone, such as strophantidin (57) and digitoxigenin (58). The chemistry of the butenolides has been extensively reviewed by Rao[71].


(56)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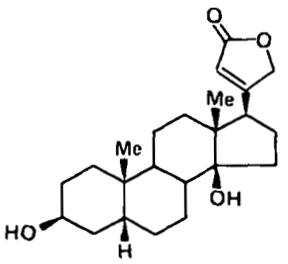
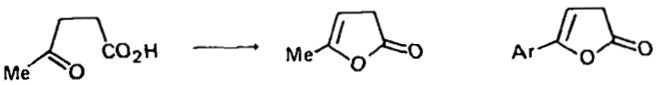
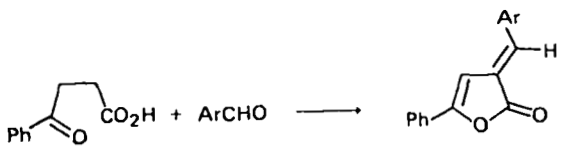

(58)

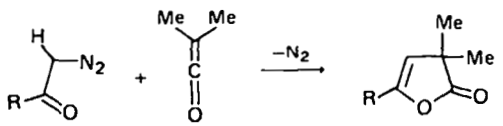
a. β,γ-Butenolides. β,γ-Butenolides, which have the enol lactone structure, are obtained from γ-keto carboxylic acids. Thus, laevulinic acid on distillation yields α-angelica lactone (59), the simplest member of this group. β-Aroylpropionic acids form γ-aryl derivatives (60) when heated with acetic anhydride[72]. When the


(59) (60)

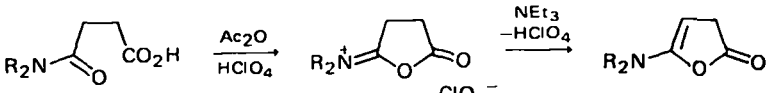
reaction is carried out in the presence of an aromatic aldehyde, α-aryl-methylene-β,γ-butenolides are produced (equation 22)[73], which in some instances


(22)

may be isolated in geometrically isomeric forms[74]. β,γ-Butenolides are also formed from diazoketones and ketens[75]; the method succeeds best with aliphatic diazoketones (equation 23). Unstable, highly reactive γ-dialkylamino-β,γ-butenolides,


(23)

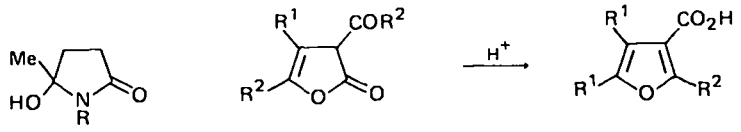
e.g. 62, are generated by the action of triethylamine on tertiary succinisoimidium perchlorates (61)[76]:



(61) (62)

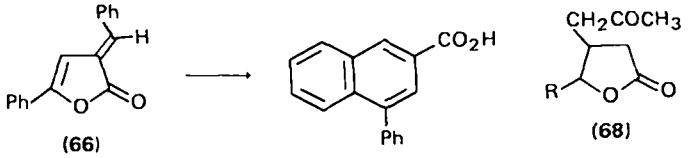
R_2N = morpholino

β,γ-Butenolides are thermodynamically unstable and tend to rearrange to the α,β isomers (see below). They can be distinguished from the latter by ultraviolet and infrared spectroscopy: the carbonyl band of β,γ-butenolides appears at 1800–1795 cm^{-1}, that of α,β-butenolides near 1750 cm^{-1}. β,γ-Butenolides are cleaved by aqueous acids or alkalis to γ-keto acids and by secondary amines to give the corresponding amides[77]. Several ring transformations are known: α-angelica lactone with primary aliphatic or aromatic amines forms 5-hydroxy-5-methylpyrrolidin-2-ones (63)[78], α-acyl-β,γ-butenolides (64) undergo acyllactone rearrangement to furancarboxylic acids (65)[79] and α-benzylidene-γ-phenyl-β,γ-butenolide (66) forms



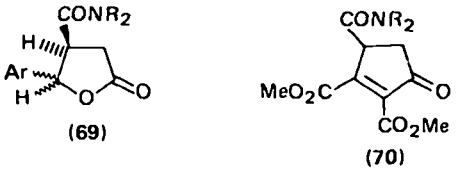
(63) (64) (65)

4-phenyl-2-naphthoic acid (67) in the presence of aluminium chloride[80] or acetic acid and hydrochloric acid[81]. The boron trifluoride-catalysed reaction of α-angelica lactone with aldehydes, RCHO, affords the acetonyl-γ-lactones (68)[82]. The



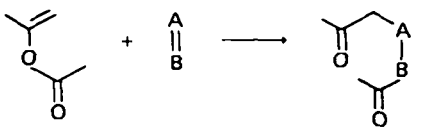
(66) (67) (68)

morpholinobutenolide (62) adds aromatic aldehydes to form mixtures of the *cis*- and *trans*-lactones 69; dimethyl acetylenedicarboxylate similarly yields the cyclopentenone 70. These reactions, which may be represented by the general equation (24), constitute analogues of the ene reaction, in which an acyl group is transferred from one component to the other[76].



(69) (70)

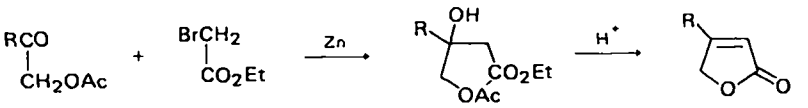
(24)



b. α,β-Butenolides. α,β-Butenolides, being more conjugated, are more stable than the β,γ isomers. α-Angelica lactone (**59**) is converted into β-angelica lactone (**71**) on repeated distillation. The conversion is catalysed by bases; industrially,

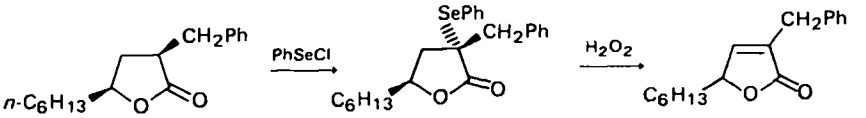
(59) (71)

Fuller's earth is used. The commonest method for preparing α,β-butenolides is the Reformatzky reaction of α-bromo esters with α-acetoxy ketones (equation 25).



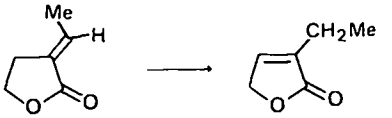
(25)

Saturated γ-lactones can be converted into α,β-butenolides by selenation, followed by oxidative removal of the phenylselenyl group (equation 26)[83]. Certain α-alky-



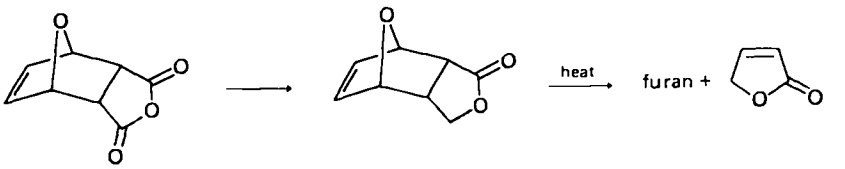
(26)

lidene-γ-lactones give butenolides on heating with deactivated Raney nickel (equation 27)[66]. α,β-Butenolide itself is best prepared by reduction of the furan–maleic



(27)

anhydride adduct with ethanolic sodium borohydride and subsequent retro-Diels–Alder fission (equation 28)[84]. The thermal decarboxylation of 1,2-diphenylcyclopropene-3,3-dicarboxylic acid yields a diphenylbutenolide (equation 29)[85].



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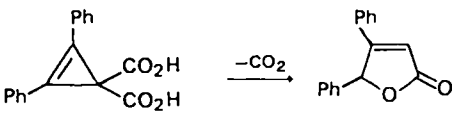
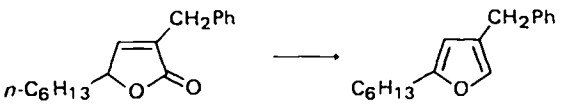


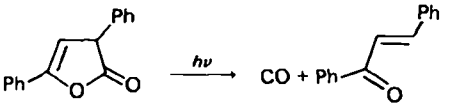
(29)

Hydrolysis of α,β-butenolides is usually accompanied by dehydration to yield unsaturated acids; reduction with diisobutylaluminium hydride gives furans, for example equation (30)[83]. However, photolysis of β,γ-butenolides results in cleavage



(30)

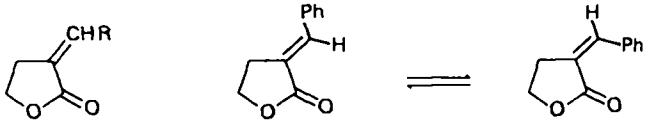
to carbon monoxide and α,β-unsaturated ketones (equation 31)[86]. α,β-Butenolides undergo a di-π-methane reaction from the triplet state to afford rearranged isomers (equation 32)[87].



(31)

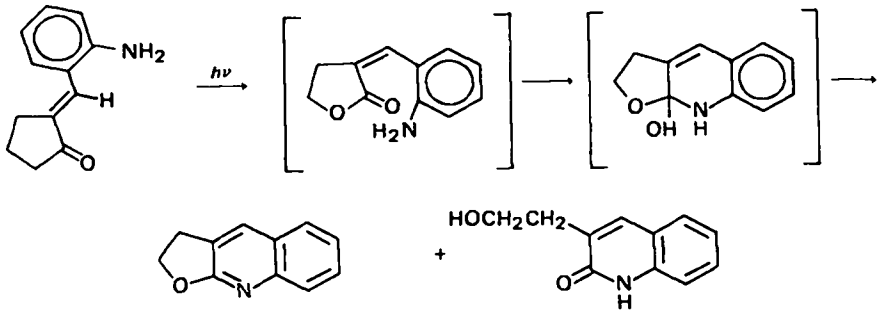
(32)

c. *γ-Lactones with exocyclic double bonds. α-Methylene-γ-lactones.* α-Alkylidene- and α-arylmethylene-γ-lactones (72) are obtained by the base-catalysed condensation of γ-lactones with aldehydes[88]. *E*-α-Benzylidene-γ-butyrolactone (73) isomerizes to the *Z* isomer (74) on irradiation; the process is reversed on heating[89].



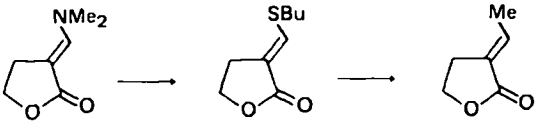
(72) (73) (74)

This reaction has been applied[90] to the synthesis of quinolinones and dihydrofuranoquinolines (equation 33). α-Ethylidene-γ-butyrolactones are produced by



(33)

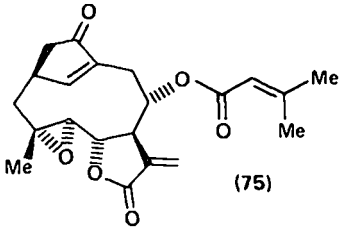
sequential treatment of (dimethylaminomethylene)-γ-lactones (53) with butanethiol and lithium dimethylcuprate[66]:



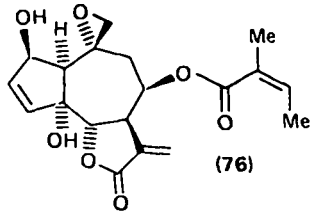
(53)

Interest in α-methylene-γ-lactones was greatly stimulated by the discovery that a number of plant sesquiterpenes of this type possessed antitumour activity. More

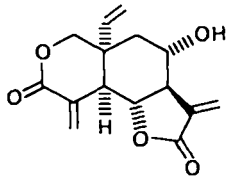
than 400 naturally occurring methylenelactones are now known[91]; biologically active compounds include elephantin (75)[92], euparotin (76)[93], vernolepin (77)[94] and helenalin (78)[95]. Much effort has been expended to develop the synthesis of α-methylene-γ-lactones[96], since even simple representatives, such as the bicyclic lactone (79) and the spiro compound (80) possess tumour-inhibiting properties[97].



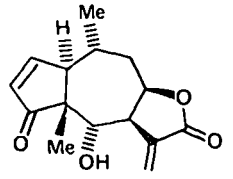
(75)



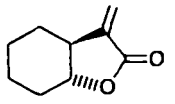
(76)



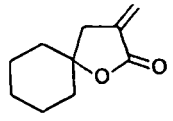
(77)



(78)

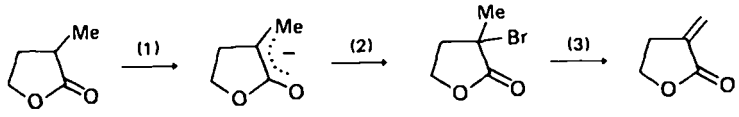


(79)



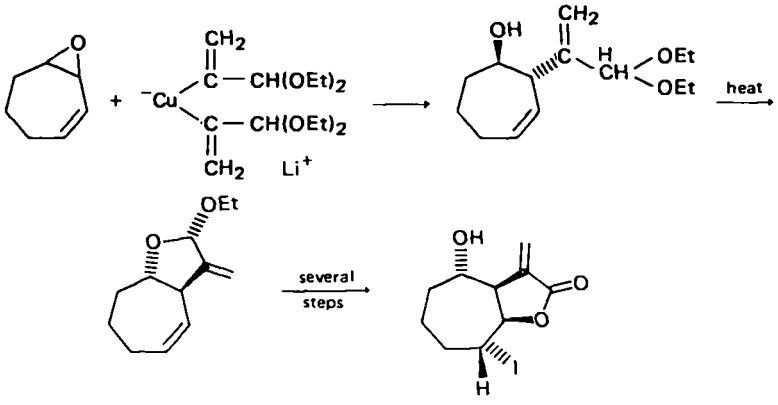
(80)

The parent compound (81) was obtained, free from the ring-unsaturated isomer, by the following sequence[98]:



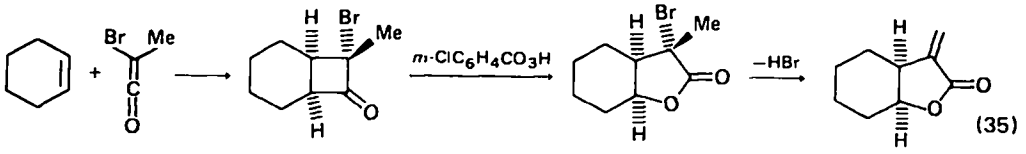
(81)

Reagents: (1) Ph_3CLi; (2) $BrCH_2CH_2Br$; (3) 1,5-diazabicyclo[4.3.0]non-5-ene.



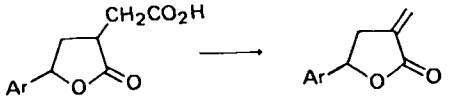
(34)

A stereospecific synthesis of methylene-γ-lactones fused to alicyclic rings uses as the key-step the reaction of epoxides with lithium dialkylcuprates (equation 34)[99]. Roberts and Ali[100] have developed a general route to bicyclic α-methylene-γ-lactones, which is based on the ring-expansion of cyclobutanones (e.g. equation 35). Another general procedure[101] is oxidative decarboxylation of (carboxy-



(35)

methyl)-γ-lactones with lead tetraacetate and copper (II) acetate in pyridine (equation 36)[102].



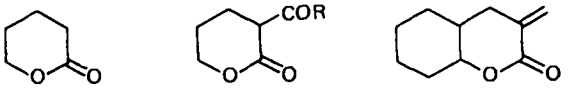
(36)

G. δ-Lactones

1. *Saturated δ-lactones and α-methylene-δ-lactones*

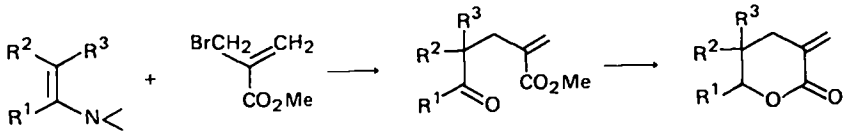
Saturated δ-lactones (82) are obtained by the general methods listed in Section II.A, and their properties have been described in Sections II.B and II.C. α-Acyl-δ-lactones (83) undergo the 'acyllactone rearrangement' (see Section II.F.1).

α-Methylene-δ-lactones, e.g. 84, are available from the corresponding (carboxy-



(82) (83) (84)

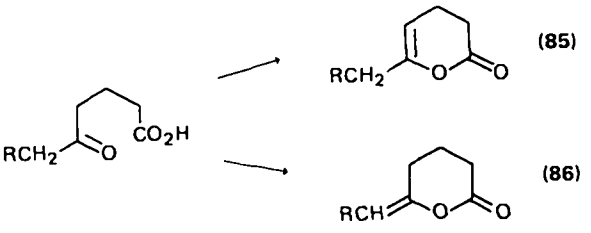
methyl) lactones (cf. equation 36)[101] and from the reaction of ketone enamines with methyl 2-(bromomethyl)acrylate (equation 37)[103]:



(37)

2. *Unsaturated δ-lactones with one endocyclic double bond*[104]

Dehydration of δ-oxo-carboxylic acids may lead to γ,δ-unsaturated δ-lactones (85) and/or δ-alkylidene-δ-lactones (86), but, in general, the isomer with the

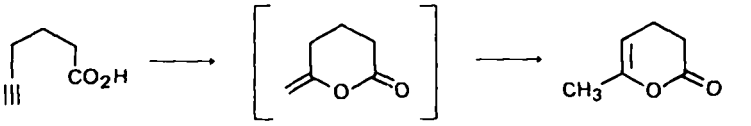


(85)

(86)

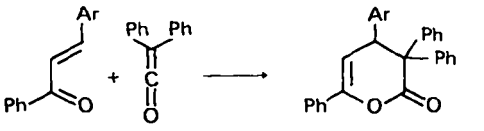
endocyclic double bond is preferred. The two types are readily distinguished by infrared spectroscopy: the former show a weak band at 1710–1695 cm^{-1}, while the latter absorb strongly at 1160–1650 cm^{-1}.

Of the three possible unsaturated systems, those with the double bond in the γ,δ-position, the enol δ-lactones (85), are best known. They can be prepared from 5-ynoic acids by the action of zinc carbonate (equation 38)[105] and by the

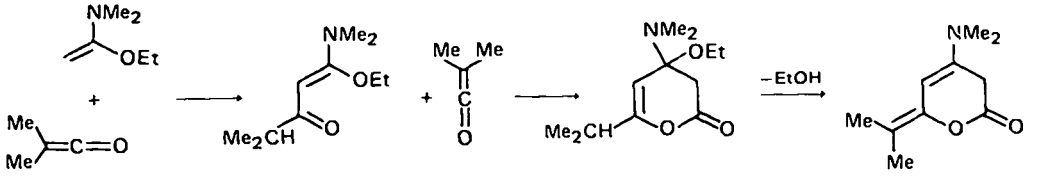


(38)

cycloaddition of diphenylketen to α,β-unsaturated ketones (equation 39). A related reaction is the formation of the δ-isopropylidene-β,γ-pentenolide (87) from 1-dimethylamino-1-ethoxyethylene and two molecules of dimethylketen (equation 40)[107].



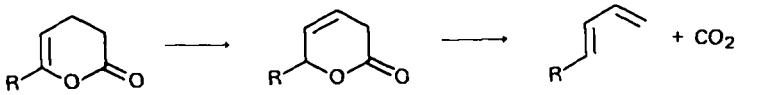
(39)



(87)

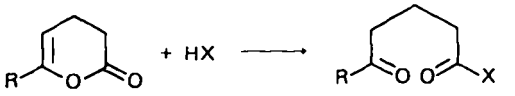
(40)

On thermolysis the enol-δ-lactones lose carbon dioxide to form 1,3-dienes; the reaction presumably involves migration of the double bond, followed by Diels–Alder reversion (equation 41):



(41)

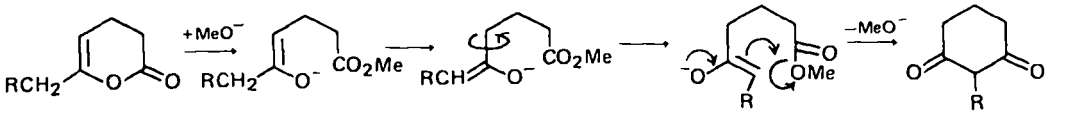
γ,δ-Unsaturated δ-lactones are more readily hydrolysed (to δ-keto acids) than the saturated counterparts. The action of alcohols and amines produces, respectively, esters and amides of δ-keto carboxylic acids (equation 42). Treatment of



(42)

X = OR, NH_2, NHR or NR^1R^2

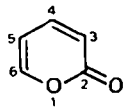
certain δ-alkyl derivatives with sodium methoxide results in cyclohexan-1,3-diones (equation 43)[108].



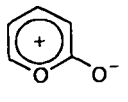
(43)

3. 2-Pyrones[109-111]

The doubly unsaturated δ-lactones (88) are known as 2-pyrones or α-pyrones. Formula 88 adequately expresses the properties of these compounds; the aromatic pyrylium oxide form (89) contributes only to a minor extent to the resonance



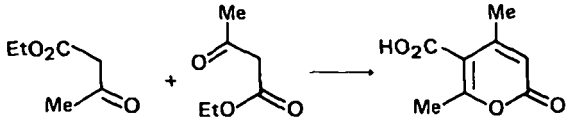
(88)



(89)

hybrid. The electronic and, in particular, the infrared spectra of 2-pyrones, which exhibit carbonyl absorption at 1735–1730 cm^{-1}, indicate that the compounds are best regarded as unsaturated cyclic esters.

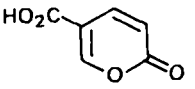
a. Synthesis. The preparation of a mixture of isodehydroacetic acid (90) and its ethyl ester by the action of sulphuric acid on ethyl acetoacetate represents a general method for obtaining the 2-pyrone system (equation 44). The formation of



(44)

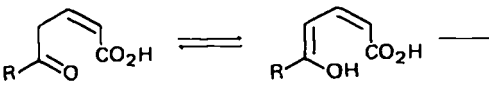
(90)

coumalic acid (91) on treatment of malic acid with sulphuric acid[112] probably proceeds in an analogous manner by way of formylacetic acid. Decarboxylation of the 5-carboxypyrones **90** and **91** yields, respectively, 4,6-dimethyl-2-pyrone and

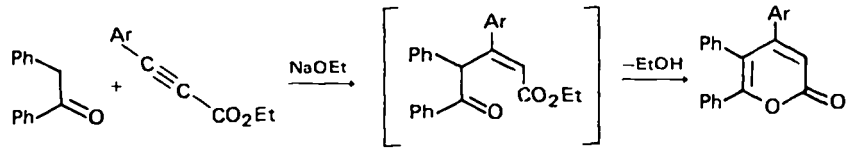


(91)

pyrone itself. Unsaturated δ-oxo acids cyclize readily to 2-pyrones (equation 45)[113]. Ruhemann's[114] pyrone synthesis is based on this principle (equation 46).

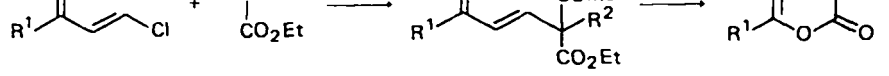


(45)



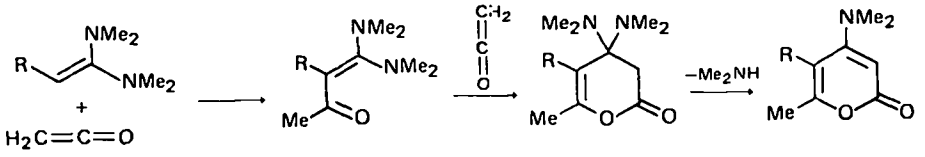
(46)

The requisite intermediate derivatives of ketonic acids can also be produced from 2-chlorovinyl ketones and β-ketonic esters (equation 47)[115]. 1,1-Bis(dialkylamino)

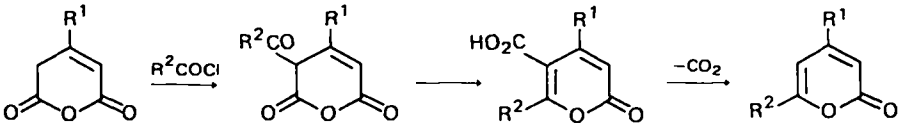


(47)

ethylenes react with two equivalents of keten to yield 4-dialkylamino-2-pyrones (equation 48)[116]. Another general synthesis is based on the rearrangement of acyl-substituted glutaconic anhydrides (92) (equation 49)[117].



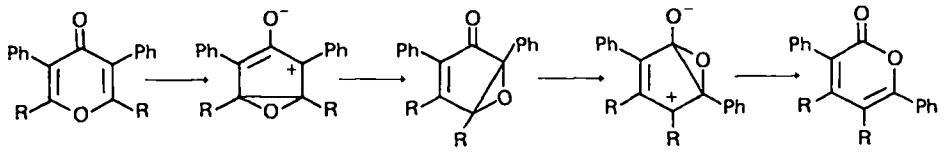
(48)



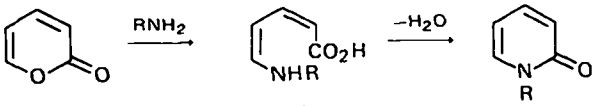
(49)

(92)

2-Pyrones are obtained in the photolysis of 4-pyrones; in this reaction the substituents remain attached to their respective carbon atoms, while the oxygen atom migrates across the ring as proposed in the following mechanism[118]:

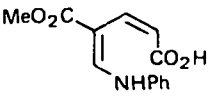


b. Properties. 2-Pyrones are stable compounds. They are chlorinated and brominated to yield 3-substituted derivatives; further halogenation occurs in position 5 if this is free[119]. Ammonia and primary amines transform 2-pyrones into 2-pyridones (equation 50); the reaction probably involves unsaturated amino acids (93) as intermediates, since a compound of this type i.e. 94, was isolated when methyl coumalate was treated with aniline[120].



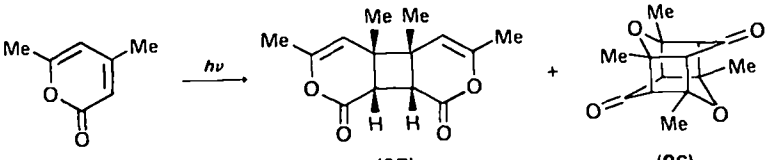
(50)

(93)



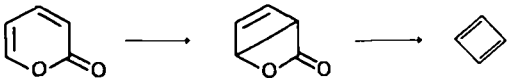
(94)

Photolysis of 4,6-dimethyl-2-pyrone yields a mixture of the *syn* dimer (95) and the cage compound (96)[121]. When 2-pyrone was irradiated in an argon matrix at



(95) (96)

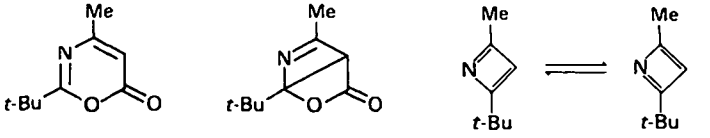
8 K, disrotatory cyclization to the β-lactone **97** occurred. Continued irradiation led to loss of carbon dioxide and formation of the elusive cyclobutadiene (equation 51)[122].



(51)

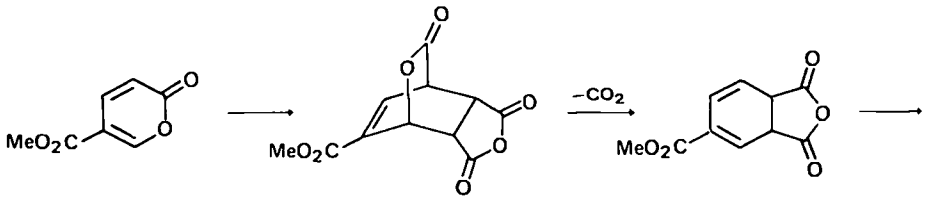
(97)

Application of this technique to the 1,3-oxazin-6-one (**98**), an aza analogue of 2-pyrone, readily gave the bicyclic lactone **99**; further photolysis led to a mixture of *t*-butyl cyanide, propyne, acetonitrile and *t*-butylacetylene. These compounds presumably originate from the fragmentation of the azetes **100** and **101**, which, however, could not be directly observed, even at 7 K[123].

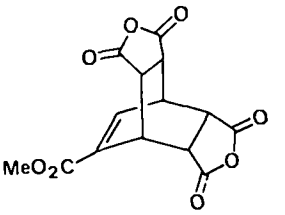


(98) (99) (100) (101)

The dienoid properties of 2-pyrones were discovered by Diels and Alder in 1931[124]. Thus, methyl coumalate and maleic anhydride form the adduct **102**, whose *endo* configuration was confirmed by dipole-moment measurements[125]. The primary adduct loses carbon dioxide at 130° and the resulting cyclohexadiene (**103**) undergoes further Diels–Alder addition to yield the 'diadduct' (**104**).

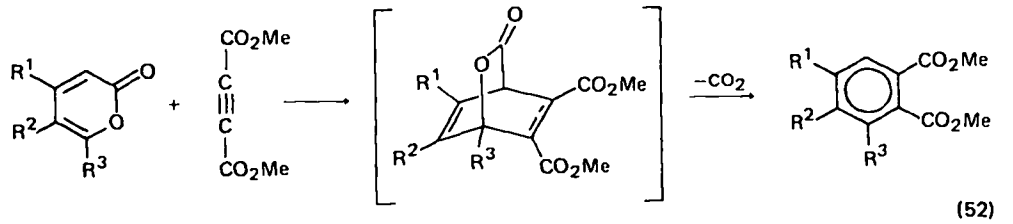


(102) (103)

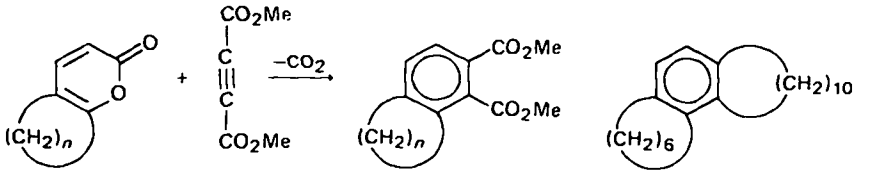


(104)

The addition of acetylenes to 2-pyrones is followed by spontaneous loss of carbon dioxide to afford benzene derivatives (equation 52)[126]: This reaction has many ramifications. Thus, treatment of the bicyclic 2-pyrones (**105**, $n = 4$ or 6) with dimethyl acetylenedicarboxylate gave the bridged phthalic esters (**106**), and a

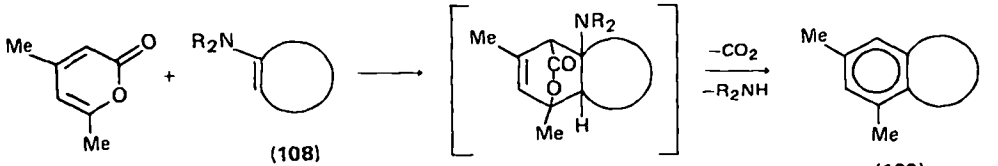


(52)



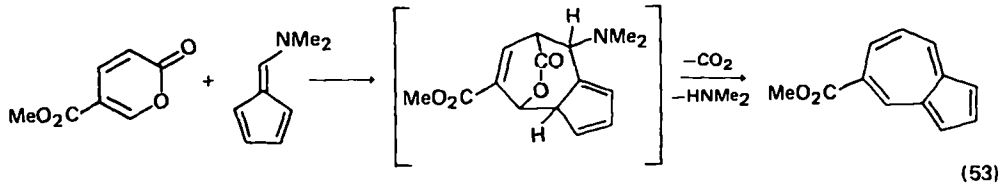
(105) (106) (107)

similar reaction of **105** ($n = 6$) with cyclododecyne led to the macrocycle (**107**)[127]. The enamines (**108**) of cyclic ketones with 6, 7, 8 or 12 carbon atoms function as acetylene equivalents in this reaction to give the benzocycloalkenes (**109**)[128]:



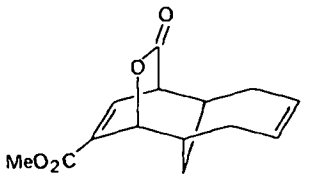
(108) (109)

A particularly elegant example is the $4\pi + 6\pi$ cycloaddition of methyl coumalate to 6-dimethylaminofulvene, which results in methyl azulene-5-carboxylate (equation 53)[129].



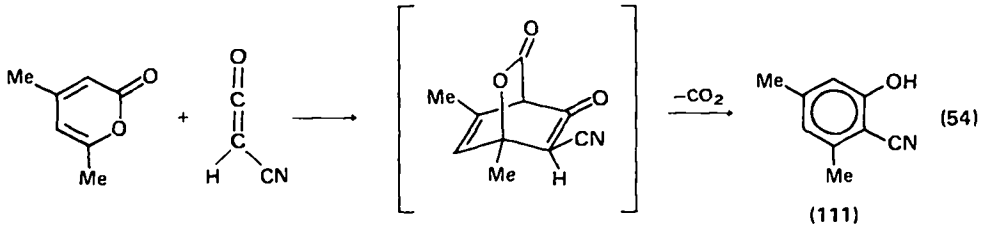
(53)

Other instances of cycloaddition reactions of 2-pyrones are the formation of the $4\pi + 6\pi$ adduct (**110**) of methyl coumalate with cycloheptatriene[130], that of the Diels–Alder product (**111**) from 4,6-dimethyl-2-pyrone with cyanoketen (equation 54)[131], and the dimerization of 2-pyrone in the presence of di-*t*-butylacetylene to yield cinnamic acid[132].



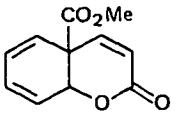
(110)

The first example of a Diels–Alder reaction, in which a 2-pyrone functions as a dienophile, is the addition of butadiene to methyl coumalate to yield **112**[133].



(54)

(111)



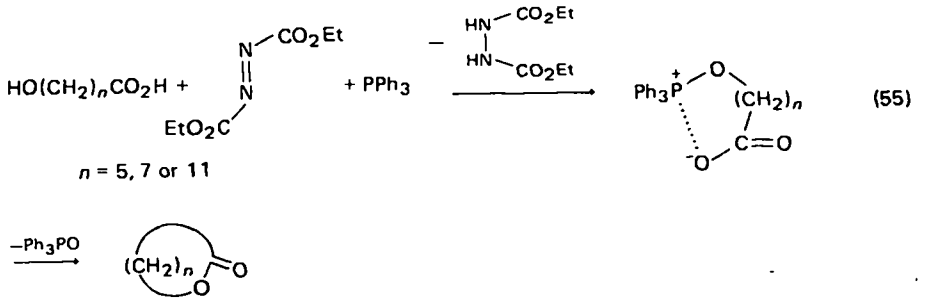
(112)

H. ϵ- and Higher Lactones

Simple lactones of ring-size 10–16 have been prepared[16,134] by treatment of ω-bromocarboxylic acids with potassium carbonate in butanone. Another general route is the ring-expansion of cyclic ketones by Bayer–Villiger oxidation[135] with organic peracids, such as *m*-chloroperbenzoic acid:

The method works well for the higher ketones[136], but cycloheptanone and cyclooctanone are less reactive and are best treated with trifluoroperacetic acid[16].

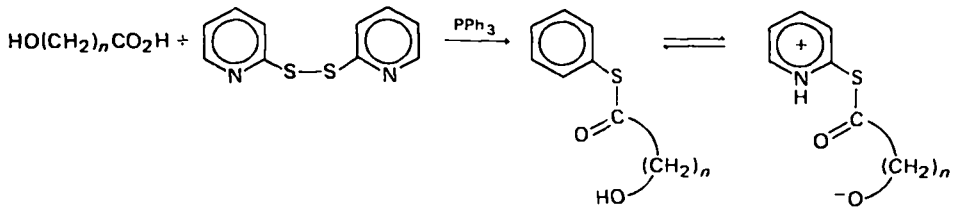
Special reagents have been developed for the lactonization of long-chain ω-hydroxy acids, such as dehydration in the presence of diethyl azodicarboxylate and triphenylphosphine (equation 55)[137], and the use of thiopyridone esters,



(55)

which on heating in xylene under conditions of high dilution undergo an 'electrostatically driven' cyclization to give macrocyclic lactones in high yield (equation 56)[138]. Dehalogenation of allylic bromides with nickel tetracarbonyl has also been used[139] for the synthesis of higher lactones, e.g. equation (57).

Macrolides are an important group of antibiotics. As this large subject has been well reviewed[140], only two representatives will be mentioned here. The



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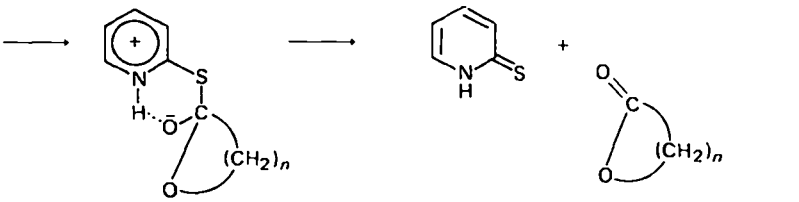
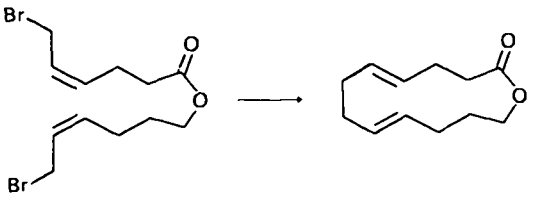
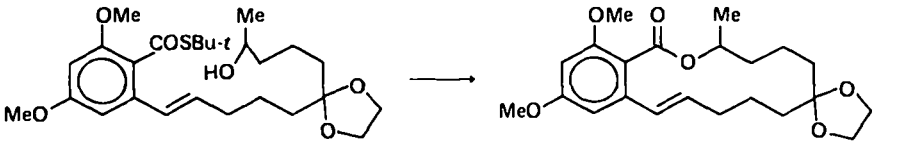




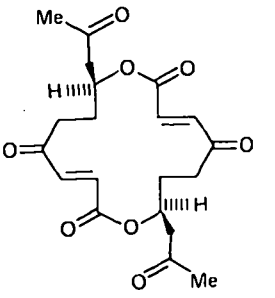
(57)

14-membered lactone, zearalenone dimethyl ether (114), was obtained[141] in 90% yield from the thio ester (113) by treatment with mercury (I) trifluoroacetate:



(113) (114)

The 16-membered macrolides are exemplified by vermiculine (115), which has been synthesized in the racemic form[142]. The configurations of these lactones have been discussed by Omura and coworkers[143].



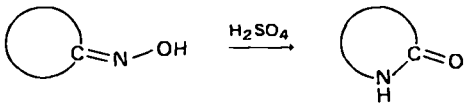
(115)

III. LACTAMS[144]

Lactams are the cyclic amides of ω-amino carboxylic acids. The seven-membered lactam, ε-caprolactam, is an important intermediate for the manufacture of Nylon; β-lactams have achieved great prominence in the last 30 years, because the antibiotic penicillins and cephalosporins contain this structural unit.

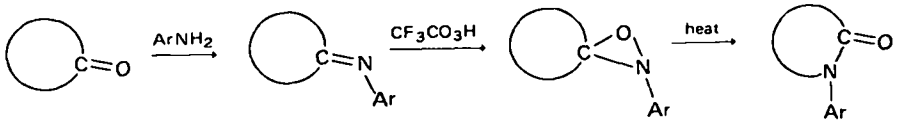
A. General Methods of Synthesis

The dehydration of ω-amino acids is only practicable for the preparation of γ- and δ-lactams. The most general synthesis of lactams of ring-size 7 and more is the Beckmann rearrangement of the oximes of cyclic ketones (equation 58).



(58)

N-Aryllactams are obtained by thermal rearrangement of 2-aryloxaziridines[145], which are readily available from cycloalkanones (equation 59).

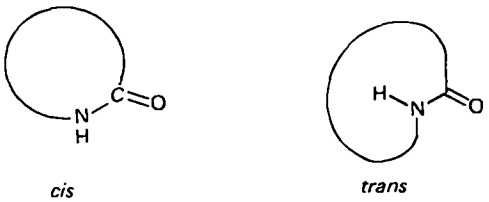


(59)

Other methods, which are less widely applicable, include the ring-transformation of lactones with ammonia[146] and the electrolytic reduction of cyclic imides[147]. Specific synthetic routes will be discussed under the appropriate headings.

B. General Physical Properties

Like lactones (see Section II.B), the smaller lactams of ring-size up to 9 are in the *cis* conformation, whereas the higher lactams exist as *trans* conformers, as do open-chain amides. This is indicated by the dielectric constants of solutions of



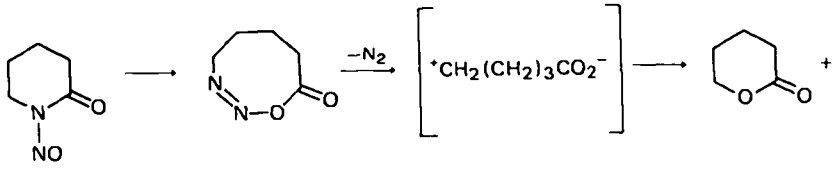
cis *trans*

lactams in benzene, which show a decrease of polarization with increasing concentration in the case of 5- to 9-membered rings, whereas the opposite is observed for lactams containing 10 to 19 atoms in the rings[148]. Likewise, the amide II band at 1520–1510 cm^{-1}, an index for the *trans* conformation of amides, is absent in the infrared spectra of chloroform solutions of 5-, 6-, 7- and 8-membered lactams, but present in those of the higher lactams from 9 atoms upwards. The 9-membered lactam is intermediate: the solid possesses the *trans* conformation, but in chloroform solution it exists as an equilibrium mixture containing 85–90% of the *cis* conformer[149]. N.m.r. studies with lanthanide shift reagents also indicate that the 8-

and 9-membered lactams prefer the *cis* structure, while the 11- and 13-membered compounds exist in the *trans* conformation; the smaller rings are largely associated[150]. Evidence for lactam association by hydrogen bonding has been obtained by dipole-moment, infrared and n.m.r. studies[151]; conformational effects on the positions and intensities of the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ bands in the ultraviolet spectra of 5- to 13-membered lactams have been investigated[152]. For reviews on ORD and CD spectra of lactams in general, see Reference 17; the circular dichroism of γ-lactams[153] and δ-lactams[154] have been discussed in detail. The mass spectra of a number of simple lactams have been determined[155].

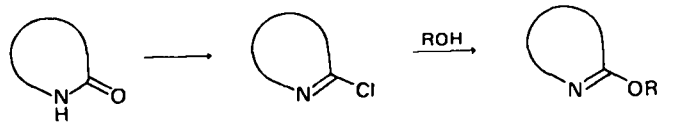
C. General Chemical Properties

Lactams are hydrolysed to amino acids; reduction with lithium aluminium hydride yields cyclic amines. The nitrogen atom in *N*-unsubstituted lactams can be alkylated, acylated, halogenated and nitrosated (with nitrous acid). The resulting *N*-nitrosolactams undergo an interesting reaction when treated with alkali (equation 60)[156].



(60)

Lactams react with phosphoryl chloride to give imidochlorides, which are converted into lactim ethers (**116**) by alcohols (equation 61). The ethyl ethers are



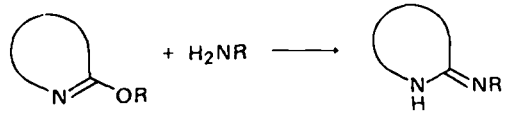
(61)

(116)

obtained more easily in one step by the action of triethyloxonium tetrafluoroborate on lactams[157]. Lactim ethers are reactive compounds, capable of a wide variety of useful transformations[158]. Thermal rearrangement results in *N*-alkyllactams (equation 62)[159]. Lactim ethers are easily reduced to cyclic

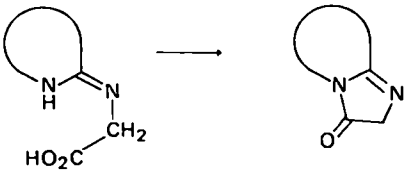
(62)

amines[159]. They react with amines, hydroxylamine, hydrazines, etc. to give amidines (equation 63). The products (**117**) from amino-acids can in certain cases



(63)

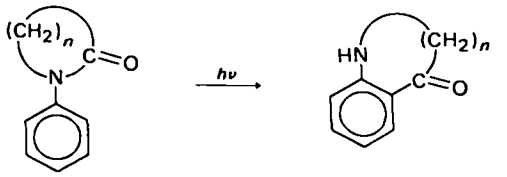
be cyclized (equation 64)[160]. Lactim ethers were key intermediates in the total synthesis of corrins[161].



(64)

(117)

Fused heterocyclic compounds are produced by the photolytic rearrangement of *N*-aryllactams (equation 65)[162]. The 2,6-xylyl analogues yield paracyclopanes for $n = 7$ or 11; the reaction fails with smaller lactams (equation 66)[163].



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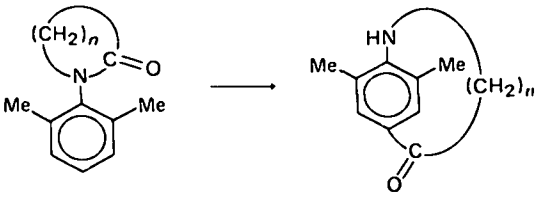
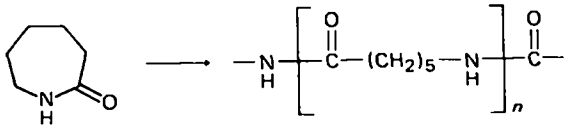


(66)

Large amounts of ε-caprolactam are produced for conversion into 'Nylon 6' ('Perlon') (equation 67). β,β-Dimethyl-β-lactam similarly gives 'Nylon 3' (equation 68). Lactam polymerization can be brought about by cationic, anionic or hydrolytic processes[164]. The subject has been reviewed by Schlack[165] and by Millich and Seshari[166].



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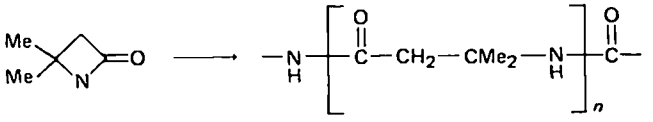
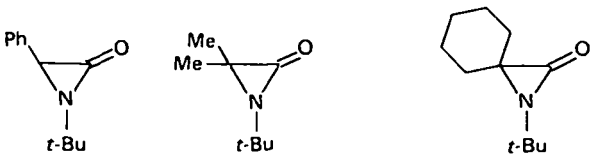


(68)

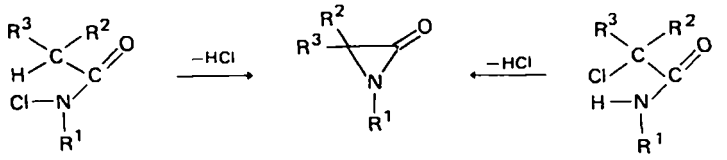
D. α-Lactams[167]

In contrast to α-lactones, compounds containing the three-membered lactam ring are readily synthesized and certain derivatives are remarkably stable. The first spectroscopic detection of a α-lactam, compound **118**, was reported by Baumgarten and his colleagues in 1961[168] and this was soon followed by the isolation of this lactam in racemic[169] and optically active forms[170]. Simultaneously and independently, Sheehan and Lengyel prepared the first purely aliphatic α-lactam (**119**)[171].



(118) (119) (120)

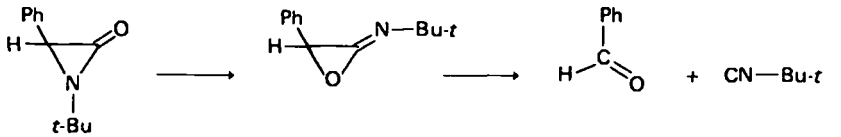
α-Lactams are synthesized by the action of potassium *t*-butoxide on *N*-chloroamides or, more successfully, on α-halo amides (equation 69).



(69)

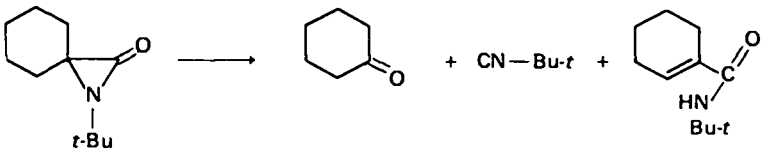
The carbonyl stretching frequency of α-lactams is found at 1850–1837 cm^{-1}. They are highly reactive compounds, which readily suffer ring-fission. The ring system is stabilized primarily by the presence of tertiary alkyl groups, e.g. *t*-butyl and 1-adamantyl, on the nitrogen atom; attachment of two alkyl groups to the α-carbon atom, as in compounds **119** and **120**[172], also enhances the thermal stability.

α-Lactams decompose on warming by at least two pathways. The *N*-*t*-butyl-α-phenyl derivative (**118**), for instance, gives a mixture of benzaldehyde and *t*-butyl isocyanide; minor amounts of benzylidene-*t*-butylamine have also been detected (equation 70)[173]. The main products are thought to be formed via a preliminary



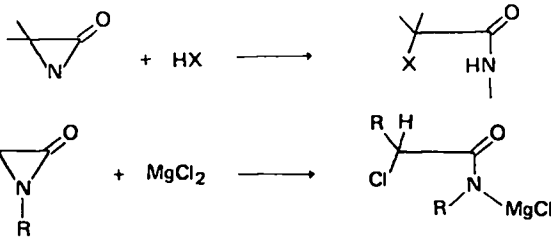
(118) (70)

rearrangement to an iminooxiridine. Spiro-α-lactams decompose in an analogous manner to cycloalkanones and isocyanides; however, these compounds yield a further type of product, an α,β-unsaturated amide (equation 71)[172,174].



(71)

Nucleophilic reagents open the α-lactam ring by rupture of either the alkyl-nitrogen bond, the acyl-nitrogen bond or the carbon–carbon bond. The mode of fission is highly specific: protic nucleophiles, such as water, alcohols, amines, thiols and mineral acids, yield amides by alkyl–nitrogen fission (equation 72). This type of reaction also occurs when di-1-adamantyl-α-lactam (**121**, R = 1-adamantyl) is

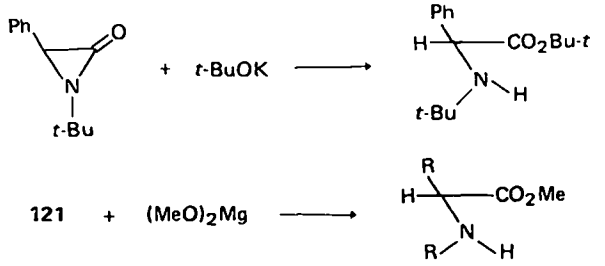


(72)

(73)

(121)

treated with magnesium halides (equation 73)[175]. Acyl-nitrogen fission, leading to derivatives of α-amino acids, is brought about by aprotic nucleophiles, e.g. equations (74)[170] and (75)[175]. Similarly, one of the six products isolated from the



(74)

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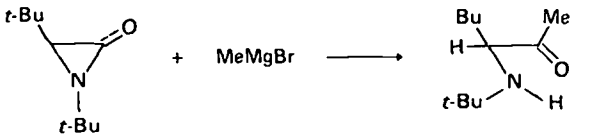
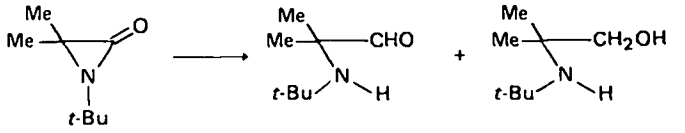
reaction of *N*,*C*-di-*t*-butyl-α-lactam with methylmagnesium bromide is a ketone (equation 76)[176]. The reduction of lactam **119** with lithium aluminium hydride to



(76)

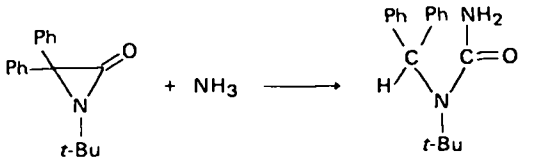
afford a mixture of an α-amino aldehyde and an α-amino alcohol proceeds analogously (equation 77)[177]. The third mode of fission, rupture of the carbon–



(77)

(119)

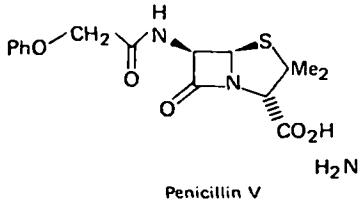
carbon bond, is only rarely observed. The major product of the reaction of *N*-*t*-butyldiphenyl-α-lactam with liquid ammonia is *N*-benzhydryl-*N*-*t*-butylurea (equation 78)[178].



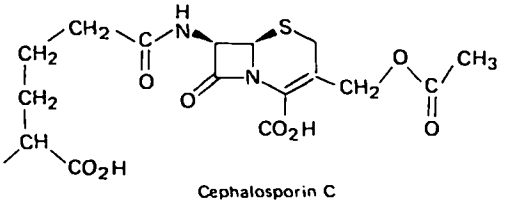
(78)

E. β-Lactams[179–181]

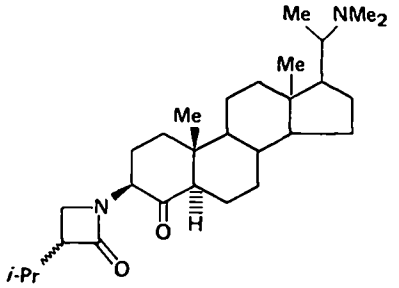
The first β-lactam was obtained by Staudinger in 1907[182]. In the course of the Anglo-American cooperation on mould metabolites during the 1939–1945 war[183] it was found that penicillin contains a β-lactam ring. Cephalosporin C, the parent metabolite of the antibiotic cephalosporins, has a related ring system. The steroidal alkaloid pachystermine A[184] and the peptide wildfire toxin[185] also possess the β-lactam structure. The excellent antibiotic properties of the penicillins, and even



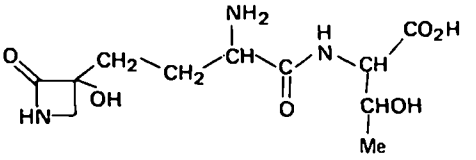
Penicillin V



Cephalosporin C



Pachystermine A

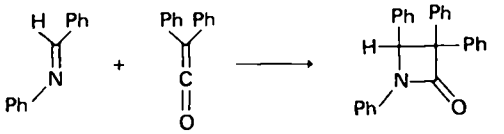


Wildfire toxin

more so of the cephalosporins, have stimulated intense efforts to synthesize analogues that would equal or surpass the natural substances in activity. Consequently, the chemistry of the β-lactams has been investigated more thoroughly than that of any other class of lactams.

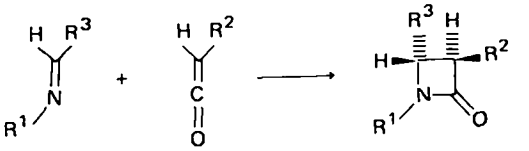
1. Synthetic methods[186,187]

Staudinger's classical synthesis[182,188] of β-lactams is the cycloaddition of ketens to Schiff's bases, e.g. equation (79). Aldoketens and monosubstituted imines



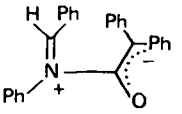
(79)

tend to give *trans* isomers (equation 80)[189]. These cycloadditions are non-concerted; thus, in the reaction of benzylideneaniline with diphenylketen (equation

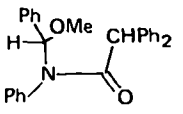


(80)

79) the dipolar intermediate (122) has been trapped by methanol as the amide (123)[190]:

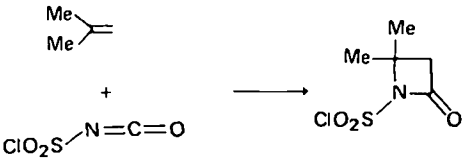


(122)



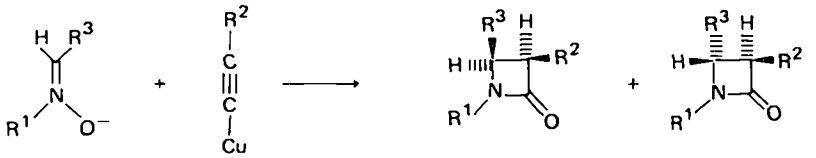
(123)

β-Lactams are formed in the cycloaddition of olefins to reactive isocyanates, such as *p*-nitrophenyl isocyanate[191] and, particularly, chlorosulphonyl isocyanate (equation 81)[192]. The products are formed by stereospecific *cis* addition to the



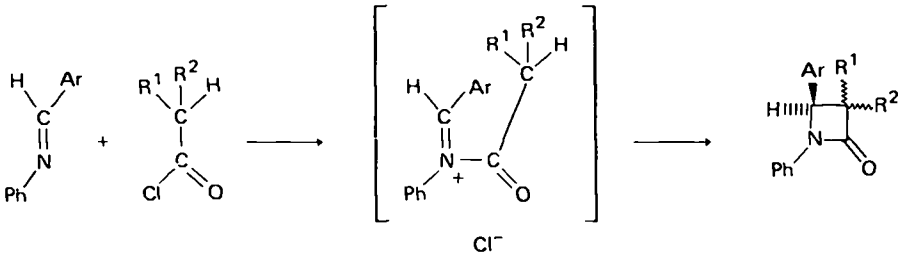
(81)

olefin, as shown by the configuration of the lactams obtained from *cis*- and *trans*-substituted olefins. Nevertheless, the reaction may proceed by a two-step polar mechanism[193].



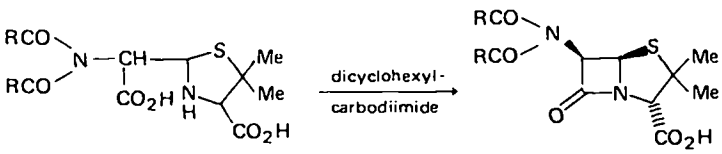
(82)

Treatment of nitrones with copper(I) acetylides in pyridine yields mixtures of *cis*- and *trans*-β-lactams (equation 82)[194]. Geometrically isomeric products are also obtained by the action of acyl chlorides on Schiff's bases (equation 83)[195].



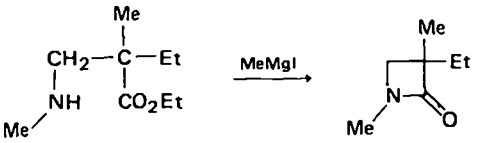
(83)

The formation of the β-lactam ring by dehydration of a β-amino acid is exemplified by Sheehan's classical penicillin synthesis (equation 84)[196]. Other

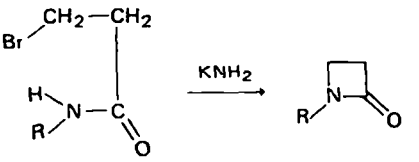


(84)

cyclizations proceed from β-amino esters (equation 85)[197] and from β-bromo amides (equation 86)[198].

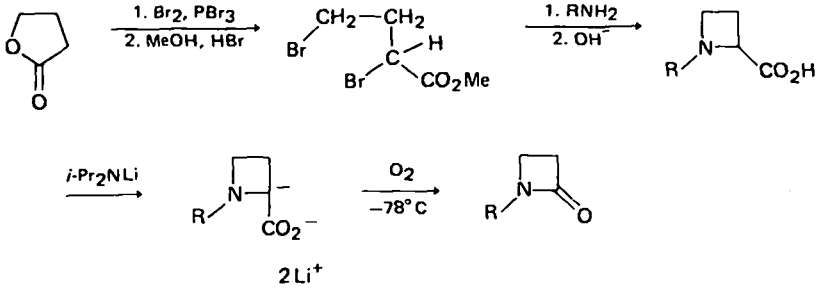


(85)



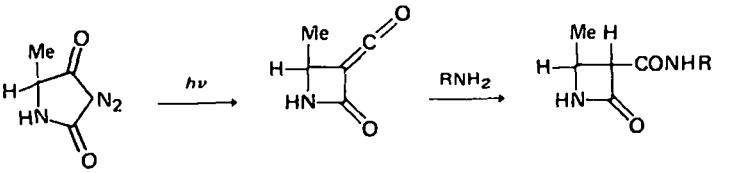
(86)

α,γ-Dibromo esters, obtainable from γ-lactones, yield azetidinecarboxylic acids, which can be oxidized to β-lactams (equation 87)[199]. The photo-Wolff rearrange-



(87)

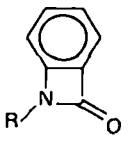
ment of 3-diazopyrrolidin-2,4-diones leads to α-carbamyl-β-lactams (equation 88)[200].



(88)

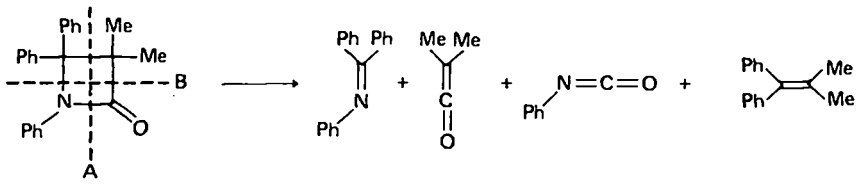
2. Properties

Simple β-lactams absorb at ca 1755 cm^{-1} in the infrared region. The four-membered ring is planar[201] and strained; the strain would be even more severe in unsaturated β-lactams. The only compound of this type appears to be the benzo derivative (**124**, R = 1-adamantyl)[202].



(124)

β-Lactams are easily hydrolysed by alkali to β-amino carboxylic acids. Thermal fission produces all possible fragments, i.e. imines and ketens by cleavage A, and isocyanates and olefins by cleavage B[188]:



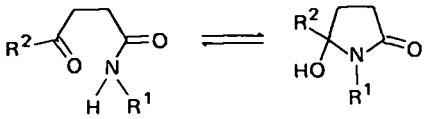
3. *Penicillins and cephalosporins*

No account of these compounds will be given here as their synthesis and chemistry has been extensively reviewed elsewhere[181,203-208]. Recent synthetic efforts have concentrated on modifying the thiazolidine and thiazine rings in these systems without disturbing the β-lactam structure.

X-Ray analysis has shown that the β-lactam ring in both penicillins[209] and cephalosporins[210] is flat. However, the carbonyl group does not lie in the plane of the ring so that normal amide resonance is suppressed, as evidenced by high-frequency carbonyl stretching bands at 1780–1770 cm^{-1} and 1776–1764 cm^{-1} in the spectra of penicillins and cephalosporins, respectively. The compounds are therefore best regarded as cyclic amino ketones.

F. γ-Lactams

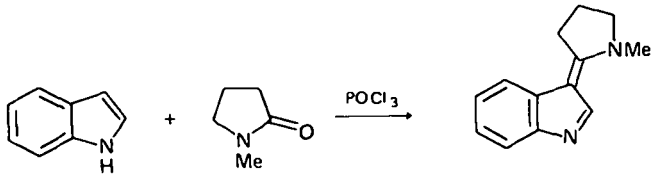
Saturated γ-lactams are obtained by dehydration of γ-amino carboxylic acids and by the action of ammonia on γ-lactones[211]. γ-Oxoamides exist in equilibrium with the cyclic tautomers, the γ-hydroxy-γ-lactams (equation 89). Studies by



(89)

infrared, ultraviolet and n.m.r. spectroscopy indicate that the composition of the equilibrium mixture depends on the nature of the substituents R^1 and R^2 and on the solvent[212,213]. β-Benzoylpropionamide and β-benzoylpropionanilide are open-chain compounds, both in the solid state and in solution.

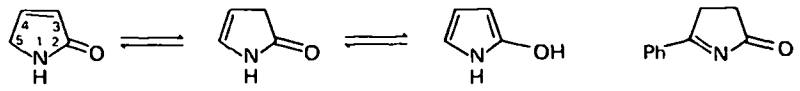
N-Methylpyrrolidone is a useful aprotic solvent; for example, for the preparation of aryl cyanides from unactivated aryl halides and copper(I) cyanide[214]. Like dimethylformamide, *N*-methylpyrrolidone can be used in the Vilsmeier–Haack reaction; thus, indole yields an indolenine (equation 90)[215]. Poly-*N*-vinyl-



(90)

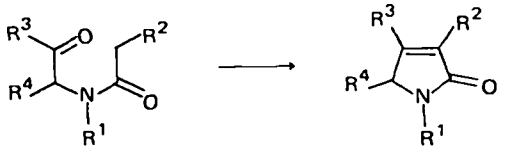
pyrrolidone is used as a blood-plasma extender and in aerosol sprays for hair-setting.

Unsaturated lactams are tautomeric with 2-hydroxypyrroles:



(125) (126) (127) (128)

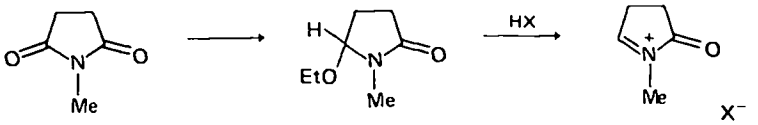
2-Hydroxypyrrole (127) itself is unstable; substituents in position 3 favour the Δ^3 pyrrolinone structure (125), while substitution at $C(_5)$ favours the Δ^4 form (126)[216,217]. The pyrrolinones are usually prepared by treatment of butenolides with ammonia or primary amines[218] or by cyclization of α-(*N*-acylamino)ketones (equation 91)[219]. 2-Phenyl-Δ^1-pyrrolin-5-one (128), a



(91)

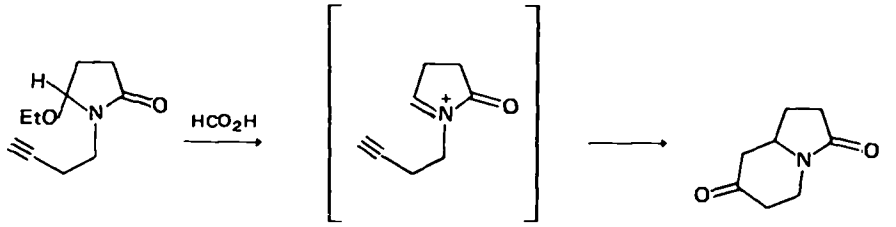
representative of a rare class of compounds, has been obtained from β-benzoylpropionamide[77].

Treatment of *N*-alkylsuccinimides with fluoroboric acid and ethanol gives γ-ethoxy-γ-lactams, which are transformed into very reactive acylimmonium cations by the action of acids (equation 92)[220]. If the *N*-alkyl group contains a

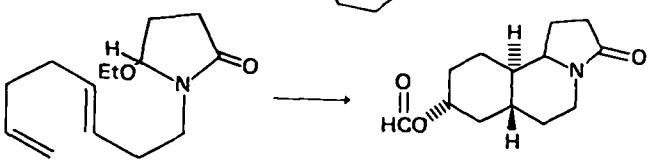


(92)

triple bond in the γ,δ- or δ,ε-position, the acylimmonium salts cyclize spontaneously (equation 93)[221]. Two carbon–carbon bonds are formed in one step from appropriate doubly unsaturated precursors equation (94)[222].



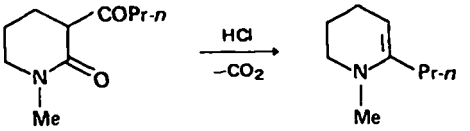
(93)



(94)

G. δ- and Higher Lactams

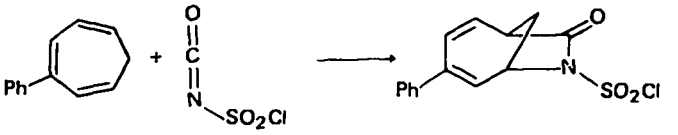
α-Acyl-δ-lactams, like the corresponding acyl-γ-lactams, undergo the 'acyllactam rearrangement' on treatment with acids (cf. Section II.F.1). α-Butanoyl-*N*-methyl-δ-lactam, for example, yields the hemlock alkaloid *N*-methyl-γ-coniceine (equation 95)[223].



(95)

ε-Caprolactam is of great industrial importance for the manufacture of 'Nylon'; it and the higher lactams[224] are readily prepared by the Beckmann rearrangement of the appropriate cycloalkanone oximes with sulphuric acid.

A bridged 8-membered lactam is formed in the cycloaddition of chlorosulphonyl isocyanate to 3-phenylcyclohepta-1,3,5-triene (equation 96)[225].



(96)

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER 9

The chemistry of orthoamides of carboxylic acids and carbonic acid

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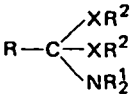
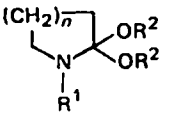
I. INTRODUCTION

The existence of orthoamides were suspected as long ago as 1887 when Busz and Kekule[1] were believed to have prepared triaminoethane by reaction of 1,1,1,-trichloroethane with secondary amines. Later investigations[2,3] however, refuted these results. In 1907 Lander[4] reported the synthesis and reactions of amide acetals that had been obtained from amide chloride and alkoxide. The chemistry of orthoamides was then neglected until the end of the fifties, when almost simultaneously Meerwein, Bredereck, Eilingsfeld, Arnold and their coworkers resumed systematic studies of the field. In the years since this revival, orthoamides have been able to gain a firm and important place in preparative organic chemistry because of their astonishing reactivity. They have been applied in many different fields as starting materials and have been the subjects of various reviews[5–8].

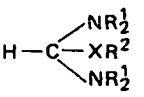
The following chapter will attempt to review the preparations and reactions of orthoamides. The following nomenclature will be used:



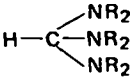
(1) X = O
Carboxylic acid amide acetals
(2) X = S
Carboxylic acid amide thio acetals



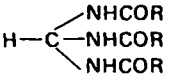
(3)
Lactam acetals



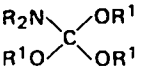
(4) X = O
Aminal esters
(5) X = S
Aminal thio esters



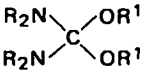
(6)
Tris(dialkyl(or diaryl)-amino)methane



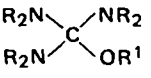
(7)
Tris(acylamino)-methane



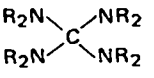
(8)
Orthocarbamic acid esters



(9)
Urea acetals

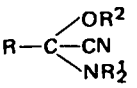


(10)
Tris(dialkylamino)-alkoxymethane

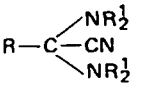


(11)
Tetrakis(dialkyl-amino)methane

Recently, α-dialkylamino-α-alkoxy nitriles (12) and α,α-bis-dialkylamino nitriles (13) have been prepared. Since their reactions are similar to orthoamides, they will be discussed in this chapter.



(12)



(13)

Heterocyclic and bicyclic orthoamide derivatives, for which reviews exist[6,9], will not be discussed. However, orthoamides which have their oxygen or nitrogen atoms bridged by alicyclic rings will be considered. See also Section VIII.

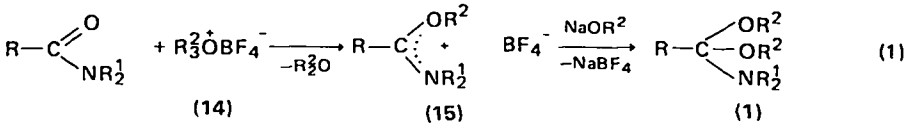
II. PREPARATION OF ORTHOAMIDES

A. Amide Acetals, Amide Thioacetals, Lactam Acetals, α-Dialkylamino-α-alkoxy Nitriles

1. *From* N,N-*dialkylalkoxymethylene iminium salts or* N,N-*dialkylalkylmercaptomethylene iminium salts*

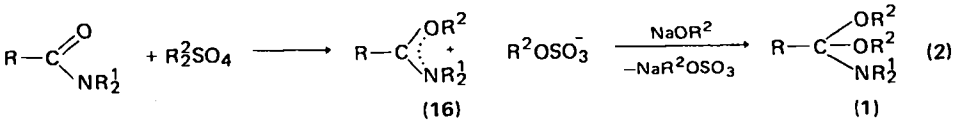
The first synthesis of amide acetals from *N,N*-dialkylalkoxymethylene iminium salts[10,11] was reported by Meerwein. According to the same procedure *N,N*-disubstituted amides were reacted with oxonium salts (14) to give iminium

salts (**15**) which were then reacted with alcoholic alcoholates to give amide acetals **1**. (equation 1). Soon after Bredereck[12] introduced a related but simpler preparative



(1)

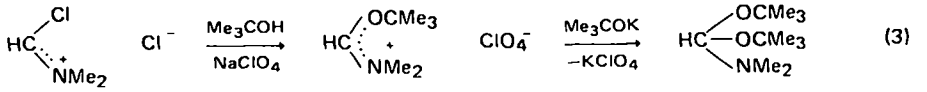
method for amide acetals. By this procedure iminium alkylsulphates(amide–dialkylsulphate adducts) (**16**), prepared from amides and dialkyl sulphates, are reacted with alcoholic alcoholate to give amide acetals (equation 2).



(2)

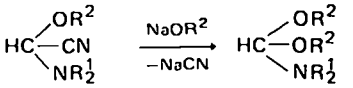
Since almost all *N,N*-disubstituted amides react with oxonium salts[13–24] to give iminium salts of type **15** (for limitations see References 13, 15 and 25), the synthesis introduced by Meerwein became generally useful. A great number of amide acetals were prepared according to this procedure[10,11,13,15,26,27]. Because of the lower alkylating ability of dialkyl sulphate, the procedure of Bredereck is not quite so general. Nevertheless a great number of iminium alkylsulphates are known[14,28–37] which have been partially transformed into amide acetals[12,26,28,36–40]. The advantage of these procedures is that cheap and easily handled alkylating agents can be used for the reaction. The yields by both procedures are comparable and are generally between 50 and 80%.

In some cases it is possible to prepare stable alkoxymethylene iminium salts from chloromethylene iminium salts and alcohols[38,41]. The product can then be converted into amide acetals[38] (equation 3). Related to these preparative methods



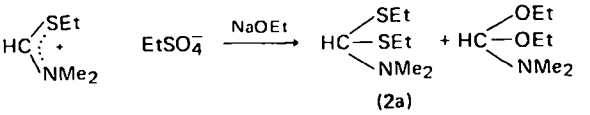
(3)

is the reaction of α-dialkylaminoalkoxy nitriles (**12a**) with alkali alcoholates in ether, which also yields amide acetals (equation 4)[42].

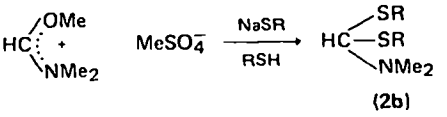


(4)

Amide thioacetals (**2**) are available from amide–dialkyl sulphate adducts[43,44] as well as from alkylthiomethylene iminium salts[43,45,46] by the action of alcoholates (equation 5) or thiolates (equations 6 and 7). The action of sodium hydride in THF on the iminium salt **17** results in 52% yield of the amide mercaptal **2c**, besides a mixture of the *cis–trans* ethylenes **18**[47]. The amide thioacetal **2d** was prepared

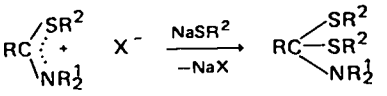


(5)



(6)

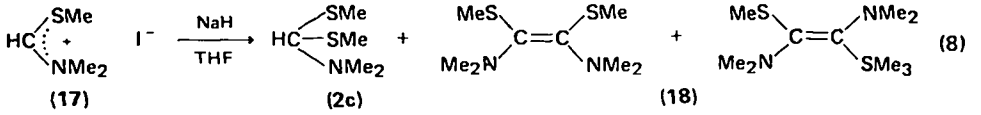
(2b)



(7)

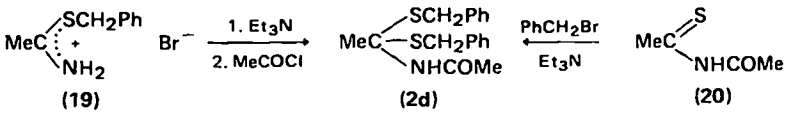
(2)

from triethylamine/acetyl chloride and the salt **19**. The route is not quite clear. The same compound was also obtained from the thio amide **20**, benzyl bromide and triethylamine[48].



(8)

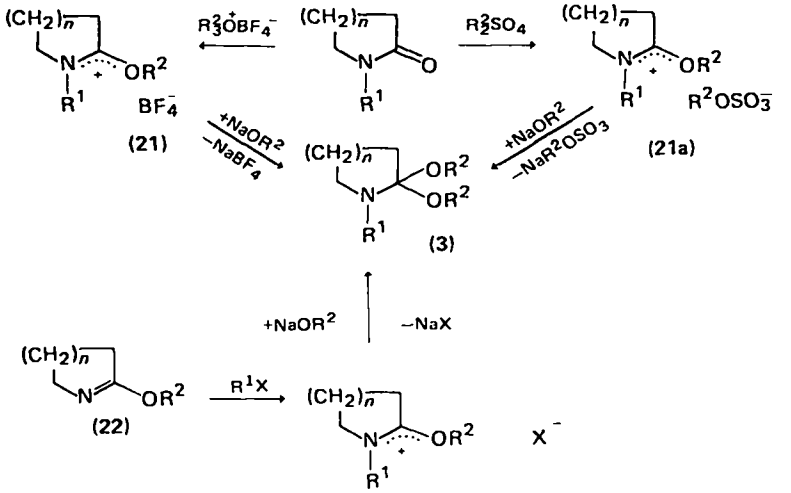
(17) (2c) (18)



(9)

(19) (2d) (20)

N-substituted lactams can be alkylated on the oxygen of the carbonyl group by oxonium salts[10,11,49,50] as well as by dialkyl sulphates[14,30,51-55]. The resulting salts **21** and **21a**, which are also available from lactim ethers **22** and alkylating agents[55,56], can be transformed by alcoholic alcoholates into lactam acetals **3**[10,11,40,53-58] (equation 10).

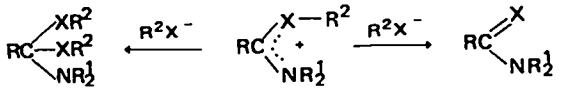


(10)

(21) (21a) (3) (22)

The limits of amide acetal syntheses are established by the ambivalent behaviour of the alkoxy- or alkylmercaptomethylene iminium salts **23**. The properties of such cations have been summarized in a review[59]. Accordingly, in the amide acetal

synthesis the thermodynamically controlled formation of ethers or thio ethers by the attack of the (thio)alcoholate on the polar $X-R^2$ bond competes with the kinetically controlled addition of the (thio)alcoholate to the carbenium carbon atom (equation 11)[13,28,44,59]. Low reaction temperatures and short reaction

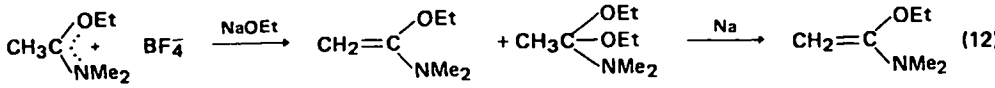


(11)

(23)

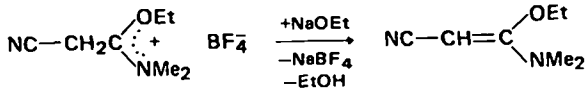
times favour the amide acetal formation while at elevated temperatures ether formation dominates. Moreover the stability and the structure of the iminium salts determine the nature of the reaction products. With very stable cations the alkoxide addition is an equilibrium reaction, so that under certain conditions it is possible to shift the equilibrium to the starting materials, so that only the thermodynamically controlled products (ether and amide) are formed[13,59]. Also, with bulky substituents (R in 23), e.g. *t*-butyl, only ether formation is observed, since steric strain during the addition of the alkoxide will favour reaction on the periphery of the iminium salt 23, namely at the polarized $X-R^2$ bond[13].

If the residue R contains α-CH bonds, they will become more acidic owing to the neighbouring positive charges, and may be attacked by the alkoxide leading to formation of ketene *O,N*-acetals together with the amide acetals[11,57]. Pure ketene *O,N*-acetals are obtained when the reaction mixture is heated with sodium[11], calcium[57] or sodium hydride[60] (equation 12).

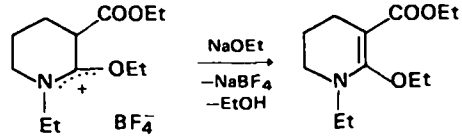


(12)

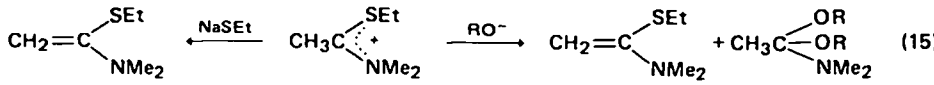
Analogous behaviour in the synthesis of α,α-unsubstituted lactam acetals was not observed[11,57]. Only when another acidifying group, like CN or COOR, is present at the α-position of the carbonium carbon, is exclusive formation of ketene *O,N*-acetals observed (equations 13 and 14).[13,56,57]. In the synthesis of amide mercaptals[61] similar observations were made (equation 15).



(13)

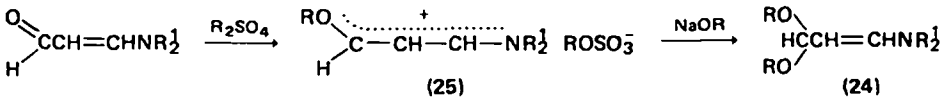


(14)



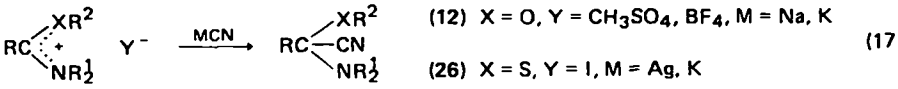
(15)

It should be mentioned that vinylogous amide acetals (24) can also be obtained from the corresponding iminium salts (25)[62,63].



(16)

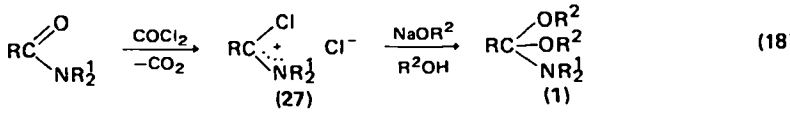
Alkoxy- or alkylmercaptomethylene iminium salts (23) react with alkali or silver cyanide to give α-dialkylamino-α-alkoxy nitriles (12)[42,64,65] or alkylthio nitriles (26)[45,66]. See also Section VII.



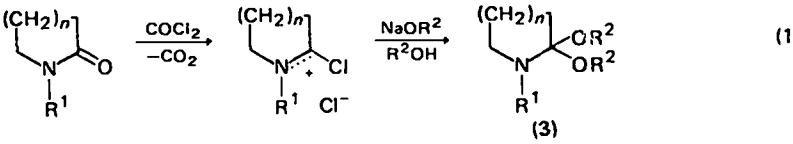
(17)

2. *From halogenomethylene iminium salts (amide halogenides) and related compounds*

Tertiary amides react easily with acylating agents like $COCl_2$, PCl_5, $SOCl_2$ and oxalyl chloride to give chloromethylene iminium chlorides[67-69] (27) which with alcoholic alcoholate solution yield amide acetals (1)[4,67,70-75] (equation 18). Lactam acetals (3) can also be obtained by this procedure[67,70-75] (equation 19).

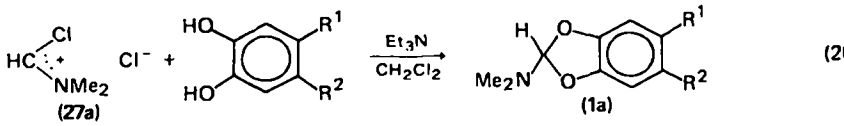


(18)

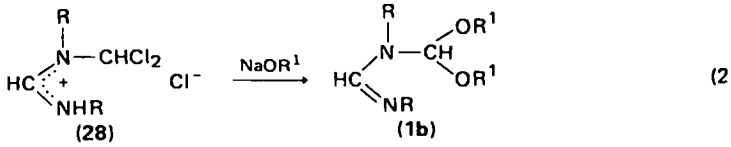


(19)

At elevated temperatures the intermediary alkoxymethylene iminium chlorides decompose easily to alkyl chlorides and amides and may alkylate alcoholates, as described in Section II.A.1. To prevent these side-reactions the working temperatures should be kept below 0°C. The yields are 30–70%. Amide acetals 1a are prepared by reaction of the salt 27a with various catechols in the presence of triethylamine[76]. The salts 28 can also be transformed into amide acetals 1b[77].

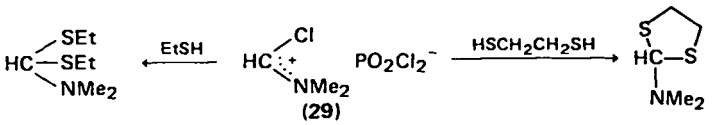


(20)



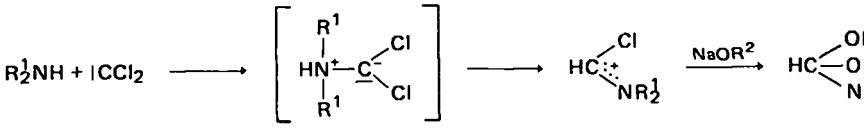
(21)

The reaction of amide–phosphoroxychloride adducts (29) with thiols is a useful procedure for the preparation of amide thioacetals[78,79] (equation 22). This method is not suitable for the syntheses of the oxygen analogues[72].



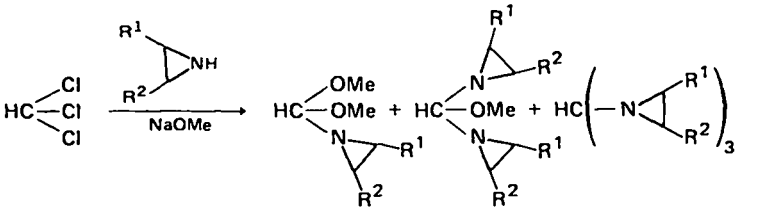
(22)

A preparative method which is generally less favourable for the preparation of amide acetals probably has a chloromethylene iminium salt as intermediate[80-82]. Dichlorocarbene, produced either from trichloroacetic acid ester[80] or from chloroform and alcoholate[81,82], is reacted with a mixture of a secondary amine and an alkali alcoholate (equation 23). Usually aminal esters and triaminomethane[81,82]



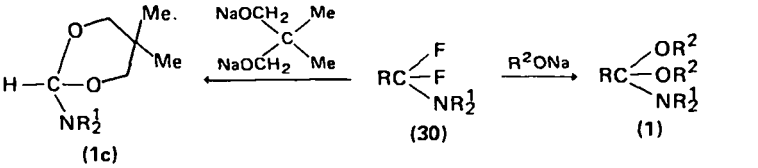
(23)

are obtained as side-products with the amide acetals, as for example in the reaction of chloroform with sodium methoxide and aziridine[82] (equation 24). On the other



(24)

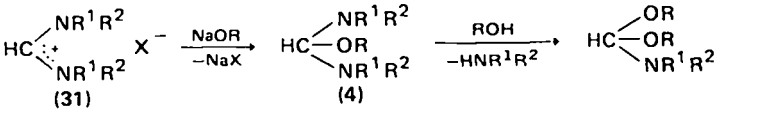
hand, the reaction of alcoholic alcoholates with the undissociated α,α-difluorotrialkylamines **30** yields the amide acetals **1c** or **1** (equation 25)[83-85].



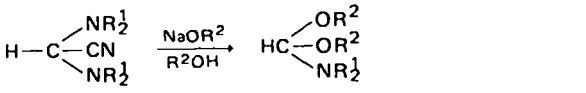
(25)

3. *From amidinium salts*

Formamide acetals are obtained by the reaction of *N,N,N',N'*-tetrasubstituted formamidinium salts (**31**) with alcoholic alcoholates through an intermediary aminal ester **4** by an alcohol–amine exchange (equation 26)[38,86-88]. The distillable α,α-bis(dialkylamino)acetonitriles react similarly (equation 27)[42]. These pro-

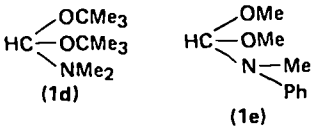


(26)



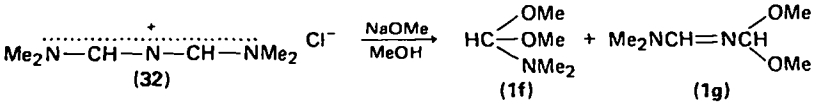
(27)

cedures are significant for the syntheses of amide acetals which contain bulky alkoxy or aryl groups on the nitrogen atoms, e.g. 1d and 1e. Alcoholic alcoholates react with the aza vinylogue of the amidinium salt 32 to give a mixture of amide

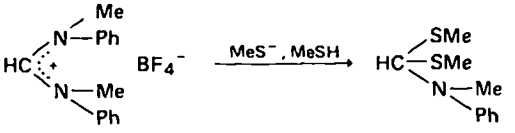


(1d) (1e)

acetals 1f and 1g[86]. Amide thioacetals are also obtained from the corresponding amidinium salts (equation 29)[88].



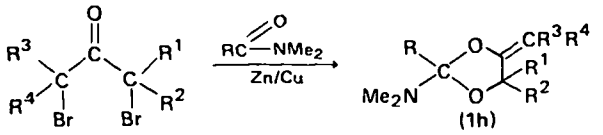
(32) (1f) (1g) (28)



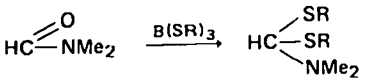
(29)

4. *Amide acetals through acetal formation from amides and related compounds*

Dimethylformamide and dimethylacetamide react in the presence of Zn/Cu alloy with 1,3-dibromo ketones to give amide acetals 1h (equation 30)[89]. Boric acid thio esters transform dimethylformamide into amide thioacetals (equation 31)[90].

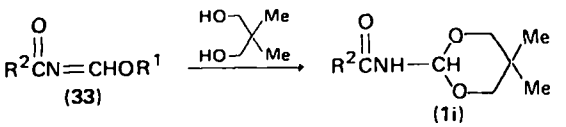


(1h) (30)



(31)

N-Acyl imino esters (33) are converted by neopentyl glycol to the *N*-acyl amide acetal 1i (equation 32)[91].

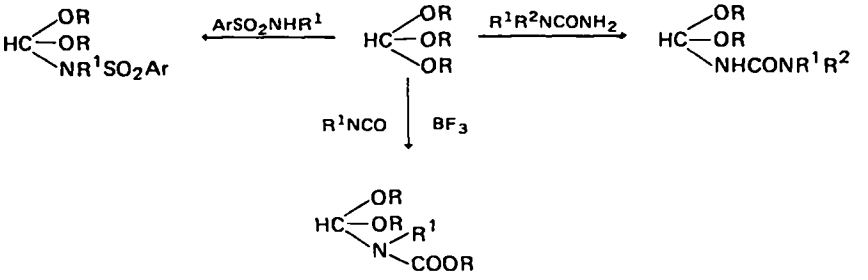


(33) (1i) (32)

5. *From orthoesters and their derivatives*

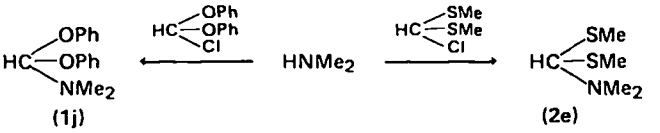
Amide acetals have been postulated as intermediates in the reactions of esters of orthoacids with primary or secondary amines[92], as well as in the condensation of orthoesters with acidic CH_2 compounds in the presence of primary amines[93–95].

Amide acetals are obtainable by the reaction of orthoesters with specific amide derivatives such as ureas[96,97] and *N*-alkyl sulphonamides[98,99] and with isocyanates catalysed by Lewis acids[100,101] (equation 33). Amide acetal **1j** or amide



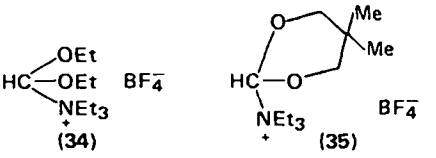
(33)

thioacetal **2e** are obtained from chlorodiphenoxymethan[102] or chlorodi(methylthio)methane[103] with dimethylamine (equation 34). With the help of the very

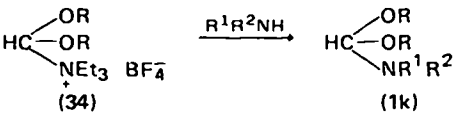


(34)

reactive dialkoxyalkyltriethyl ammonium fluoroborates, **34** and **35**[104], a number of interesting amide acetals have been prepared[91,105–107]. By reaction of salts **34**



with secondary alkyl, aralkyl and aromatic amines, amide acetals **1k** have been prepared[105]. This reaction (equation 35) will probably become important for the



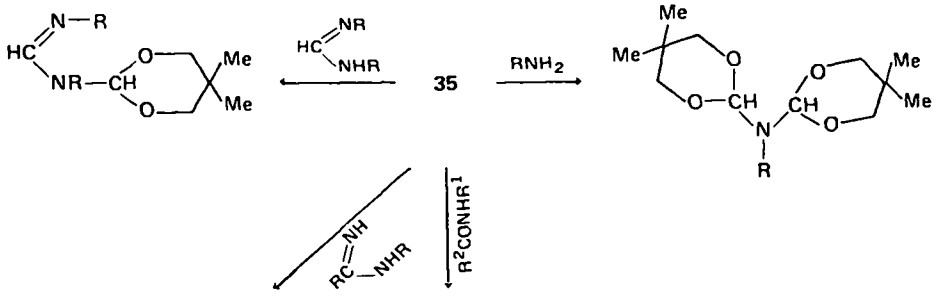
(35)

syntheses of *N,N*-diaryl amide acetals. Similarly, primary amines[107], primary amides[106], amidines[107] and secondary amides[106] can be singly or doubly dialkoxymethylated (equation 36).

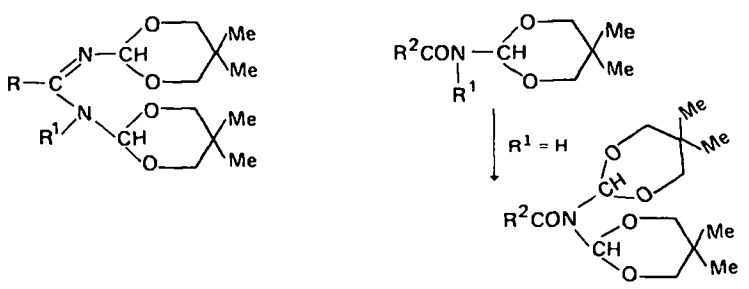
See also Section VII.

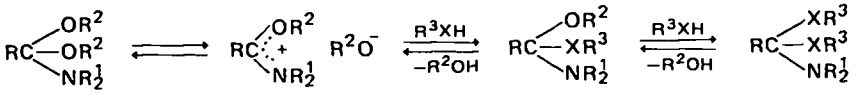
6. *From orthoamides, ketene* O,N-*acetals and related compounds*

Amide acetals are, as was shown by conductivity measurements[11,108], dissociated into alkoxymethylene iminium ions and alcoholate anions. Therefore, it is clear why acetal and amine exchanges are generally easily possible even without a catalyst (equation 37). Very pure amide acetals are obtained by acetal exchanges.



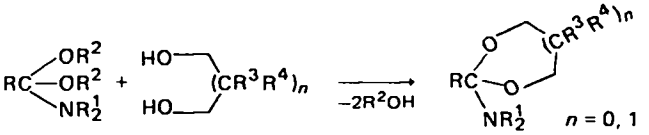
(36)





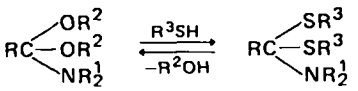
(37)

This procedure is most important for the synthesis of amide acetals containing long alkoxy groups. A large number of amide acetals have been prepared by this method[11,26,28,38,109]. Since this reaction reaches an equilibrium, completion is attained by distillation of the volatile alcohol formed. Nevertheless, bulky alkoxy groups like *t*-butyloxy[38] or some benzyloxy[26,109] groups could not be introduced through acetal exchange. When glycols are used in the acetal exchange, 2-dialkylamino dioxanes and dioxolanes are obtained (equation 38).[11,28,36,38].

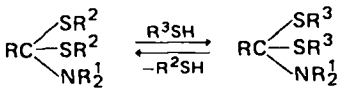


(38)

Thiols react with amide acetals to give amide thioacetals[43-45,110-113]. Amide thioacetals could also undergo acetal exchanges with thiols and they react with alcohols to give *O,O*-acetals[44] (equations 39 and 40).

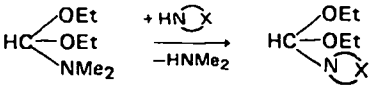


(39)



(40)

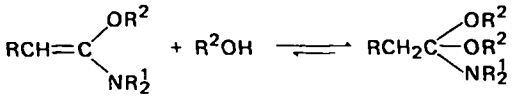
With high-boiling amines like morpholine, piperidine[11], pyrrolidine and 2,5-dimethylpyrrolidine[114], the amide acetal **11** can undergo transamination (equation 41). Analogous reactions are also performed on the corresponding thioacetals[44].



(41)

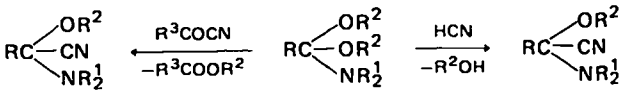
(11)

Ketene *O,N*-acetals add alcohol to form amide acetals (equation 42)[11,57]. This reaction has no preparative importance since ketene *O,N*-acetals are easily obtained from amide acetals[11,57].



(42)

Amide acetals are converted into α-dialkylamino-α-alkoxyacetonitriles **12** by hydrocyanic acid[84,115,116] as well as by acyl cyanides[64] (equation 43).

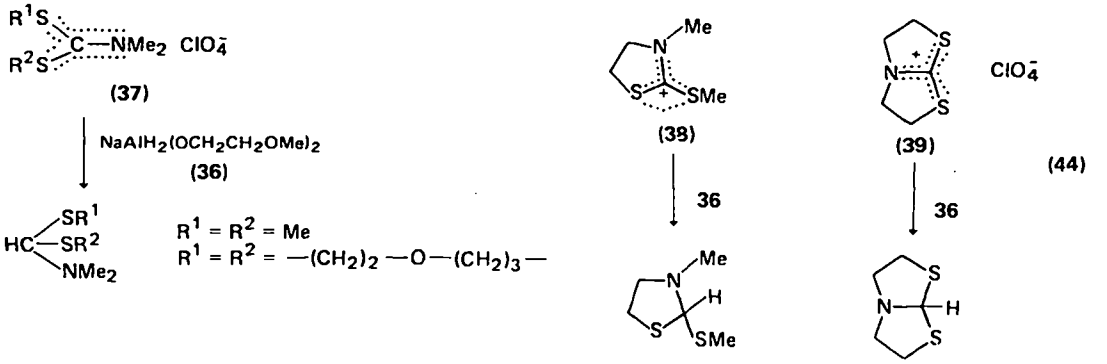


(43)

(12) (12)

7. *Amide acetals by reduction of iminium salts*

The complex aluminium hydride **36** in THF reduces the di(alkylthio)methylene iminium salts **37**, **38** and **39** to the corresponding amide thioacetals[117].



(37) (38) (39)

(36) 36 36

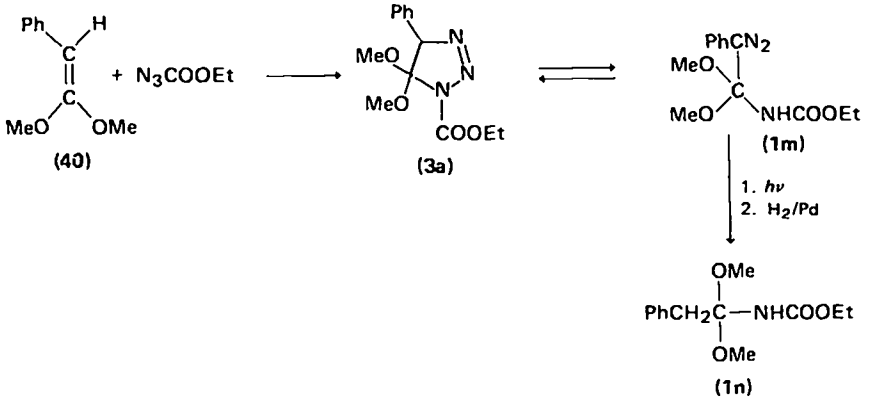
(44)

$R^1 = R^2 = Me$

$R^1 = R^2 = -(CH_2)_2-O-(CH_2)_3-$

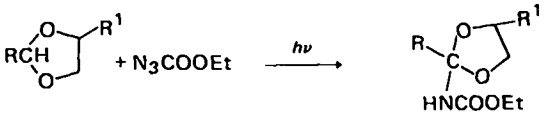
8. *Other procedures for the synthesis of amide acetals*

By the reaction of ketene acetals **40** with azidoformate, amide acetal **1m** is formed, which is in equilibrium with the triazoline **3a**[118]. By photolysis and catalytic hydrogenation the amide acetal **1n** was isolated from the reaction mixture[119] (equation 45).



(45)

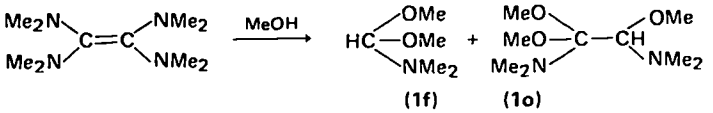
The photolytic amide acetal synthesis from dioxolanes and azidoformates can be explained as a nitrene insertion (equation 46)[120].



(46)

The methanolysis of tetrakis(dimethylamino)ethylene leads through a complex reaction to amide acetals **1f** and **1o** among other products (equation 47)[121].

See also Section VII.

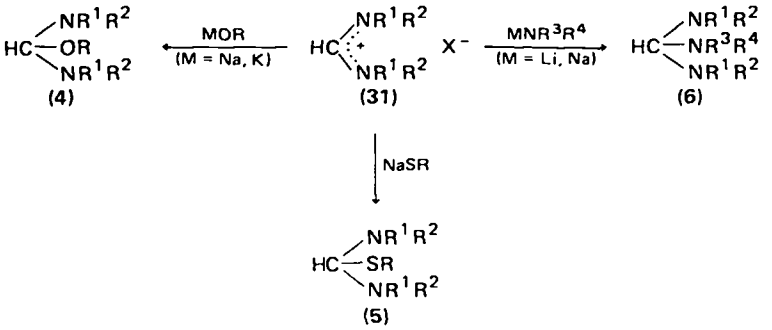


(47)

B. Aminal Esters, Triaminoalkanes and α,α-Bis(dialkylamino) nitriles

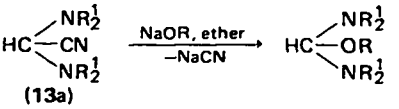
1. From N,N,N′,N′-tetrasubstituted formamidinium salts

The most favourable preparative method for the synthesis of aminal esters, aminal thio esters and tris(dialkylamino)methanes uses *N,N,N′,N′*-tetrasubstituted formamidinium salts (**31**) as starting materials. With alkali alcoholates the aminal ester 4[28,58,88,122-127] is obtained, with alkali thiolates the aminal thio esters 5[43] and with alkali metal amides the tris(dialkylamino)methanes 6[38,88,128,129] are



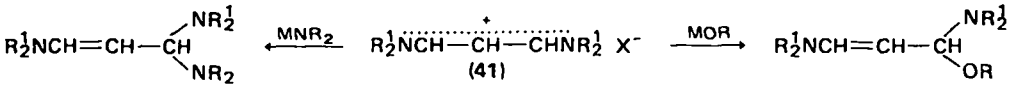
(48)

obtained. The formamidinium salts could be advantageously replaced by the easily accessible α,α-dialkylaminoacetonitriles **13a** for the synthesis of aminal esters (equation 49). Vinylogue of **4** and **6** can be prepared from the vinylogous



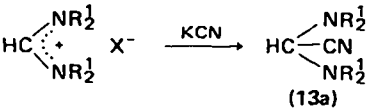
(13a) (49)

amidinium salts **41** (equation 50)[62,63]. *N,N,N',N'*-tetraalkylformamidinium salts react with alkali cyanides to give α,α-bis(dialkylamino)acetonitriles **13a** (equation 51)[64].



(41)

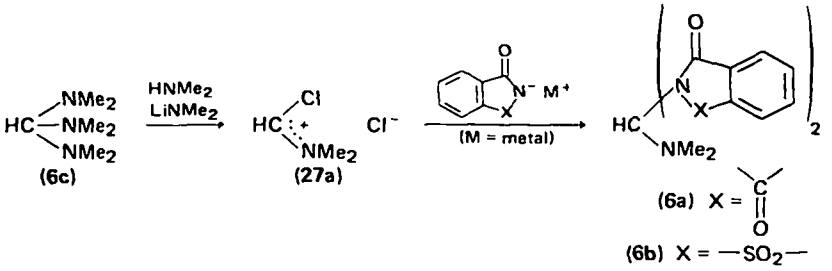
M = metal (50)



(13a) (51)

2. *From chloromethylene iminium salts and trihalomethanes; adducts of amides with acylating or alkylating agents*

The *N,N*-dimethyl chloromethylene iminium chloride **27a** reacts with potassium phthalimide[2], sodium saccharin[2] or dimethylamine/lithium dimethylamide to give the triaminomethanes **6a**, **6b** and **6c**. Trihalomethanes, e.g. chlorodifluoromethane,

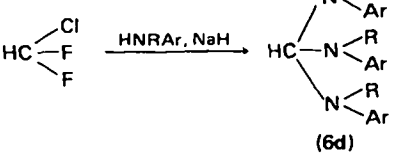


(6c) (27a) (52)

(6a) X = C(=O)

(6b) X = $-SO_2-$

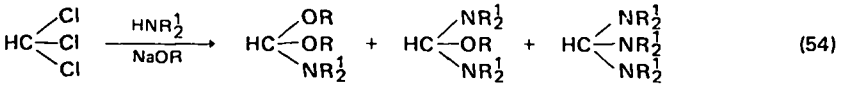
dichlorofluoromethane and chloroform react with sodium hydride and *N*-alkylanilines to give triaminomethanes **6d**. With chlorodifluoromethane the reaction proceeds homogeneously (equation 53)[88,124]. Similarly, tris(*N*-methyl-*N*-phenyl-



(6d) (53)

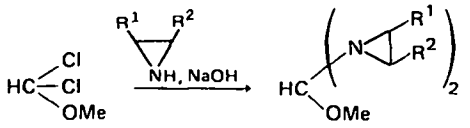
amino)methane is obtained from sodium trichloroacetate and *N*-methylaniline, probably through a dichlorocarbene[88]. Chloroform reacts with secondary aliphatic

amines[80,81] or aziridines[82] in the presence of alkali alcoholates to give a mixture of amide acetal, aminal ester and triaminomethane (equation 54). On the other



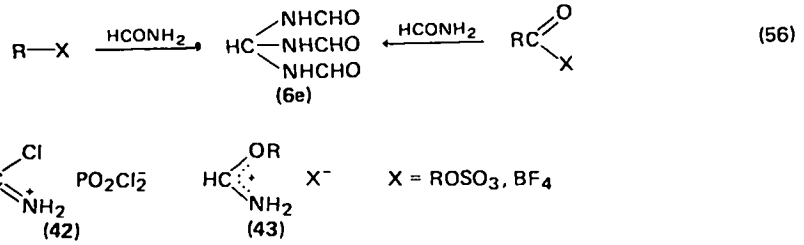
(54)

hand, the reaction of dichloromethyl methyl ether with aziridines and sodium hydroxide leads solely to aminal esters (equation 55)[82]. Besides other compounds,



(55)

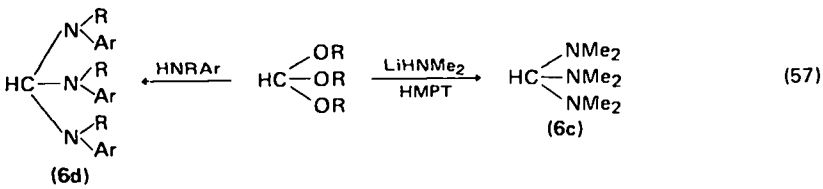
triaminomethanes have been prepared from chloroform[130] and secondary amines, using phase-transfer catalysts. Acylating agents like $POCl_3$, PCl_3, SO_2Cl_2 and acid chlorides as well as alkylating agents like dialkyl sulphates, alkylsulphonates and oxonium salts react with formamide to give tris(formylamino)methane **6e**[131-133] (equation 56). Intermediary products of the Vilsmeier–Haack type, e.g. **42** and **43**, are assumed.



(56)

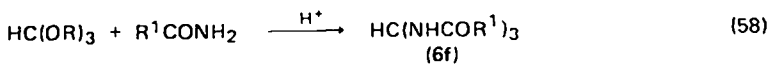
3. *From orthoesters and their derivatives*

Lithium dimethylamide, which is produced *in situ* from lithium and dimethylamine in HMPT, reacts with orthoformates to give **6c**[134]. The triaminomethane **6d** was obtained from orthoformates and *N*-methylaniline[88,124]. Other authors[135,136] formulated the reaction products of *N*-alkylanilines and orthoformates as tetraaminoethylenes (for a summary on similar reactions, see Reference 137). However, new investigations seem to show that at least in some cases the products are really triaminomethanes[81].



(57)

Under acid catalysis orthoformates react with primary amides[138,139] and urethanes[140] to tris(acylamino)methanes **6f** (equation 58). Thermal decomposition



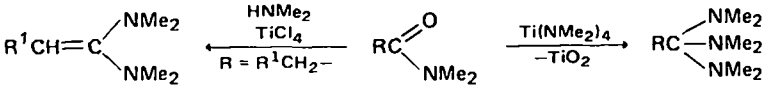
(58)

of *N*-dialkoxymethylated primary amides[43], also provides, among other products, tris(acylamino)methanes **6f**[91] (equation 59).

$$3\,R^1CONHCH(OR)_2 \xrightarrow{\Delta} HC(NHCOR^1)_3 + 2\,HC(OR)_3 \qquad (59)$$
(6f)

4. From amides

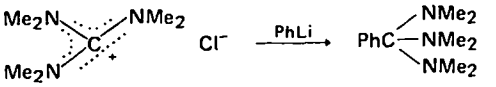
Tetrakis(dimethylamino)titanium reacts with amides which do not have α-CH bonds[141–143] to give tris(dialkylamino)alkanes[141–143]. Amides containing α-CH bonds yield under similar conditions ketene aminals or amidinium salts[144].



(60)

5. From guanidinium salts

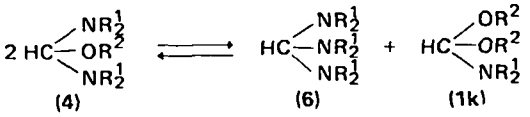
Phenyllithium reacts with *N,N,N',N',N'',N''*-hexamethylguanidinium chloride to yield tris(dimethylamino)phenylmethane (equation 61)[145].



(61)

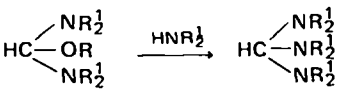
6. From orthoamides

Aminal esters 4 dismutate in the presence of traces of alcoholic catalysts[28,88] into amide acetals **1k** and triaminomethanes **6**[28,88,108,125]. This reaction (equation 62) can be used for syntheses of triaminomethanes only if the physical



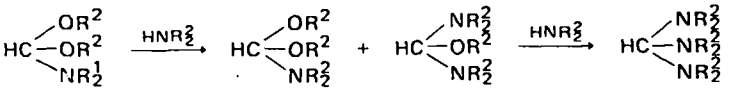
(4) (6) (1k) (62)

characteristics of **1k** are significantly different from those of **6**. From the reaction of aminal esters with secondary amines, triaminomethanes can be obtained more easily (equation 63)[126]. Transamination of amide acetals leads to aminal esters as



(63)

by-products[114] and in some cases gives good yields of triaminomethanes (equation 64)[81]. Tris(formylamino)methane **6e** can be 'transacylated' by anhydrides

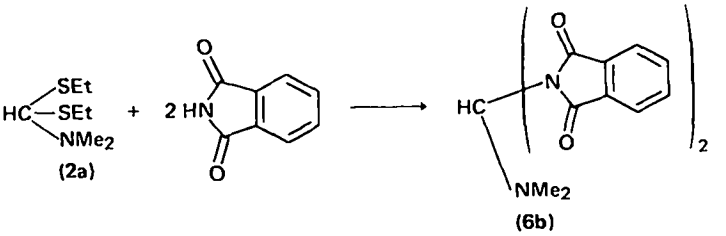


(64)

(equation 65)[132,133]. The amide mercaptal **2a** reacts with phtalimide to give the triaminomethane **6b** (equation 66)[44].

$$HC(NHCHO)_3 \xrightarrow{(RCO)_2O} HC(NHCOR)_3 \quad (65)$$

(6e)

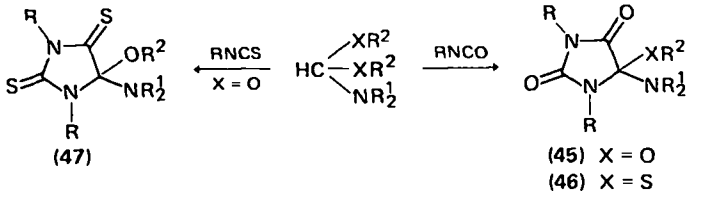


(66)

(2a)

(6b)

Dimethylformamide acetals[146,147] or thio acetals[39] react with isothiocyanates or isocyanates to yield orthoamides of parabanic acid (45 and 46) or dithioparabanic acid (47) (equation 67).

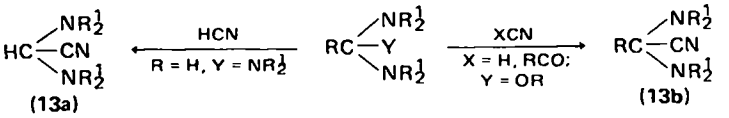


(67)

(47)

(45) X = O
(46) X = S

Aminal esters are cleaved by HCN[115,116] or by acyl cyanides[64] to give α,α-bis(dialkylamino) nitriles 13a or 13b (equation 68). Analogous cleavages of

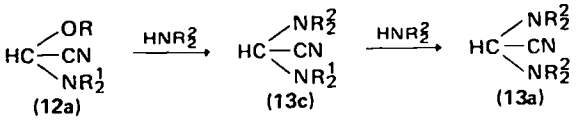


(68)

(13a)

(13b)

triaminomethanes by HCN are also known[116,148]. Dialkylaminoalkoxy acetonitriles 12a and secondary amines give mixed α,α-bis(dialkylamino) acetonitriles 13c. Excess of amine gives transamination to yield a symmetrically substituted α,α-bis(dialkylamino) acetonitrile (13a)[64,84,114,149] (equation 69). Similar observations were made in the orthooxalic acid series (equation 70)[15]. Hydro-

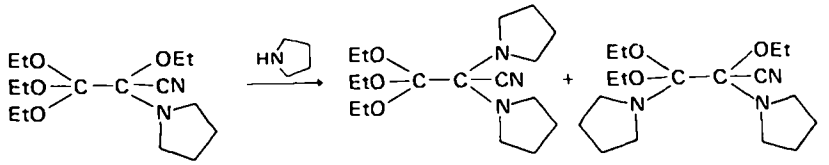


(69)

(12a)

(13c)

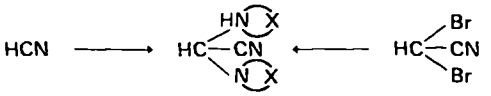
(13a)



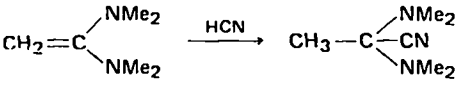
(70)

cyanic acid reacts with alicyclic amines such as pyrrolidine, piperidine and morpholine to give , -bis(dialkylamino) acetonitriles 13d[148,150]. α,α-Dimorpholinoacetonitrile may also be prepared from dibromoacetonitrile and morpholine[151]

(equation 71). The addition of HCN to ketene aminals also leads to α,α-bis(dialkylamino)alkylnitriles[115,166] (equation 72).



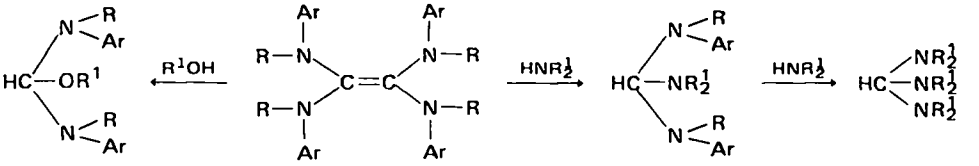
(13d)



(72)

7. Other methods

Tetraaminoethylenes react with alcohols or amines and amine derivatives to give aminal esters[152,153] or triaminomethanes[154,155] (equation 73). These reactions were recently summarized[156].

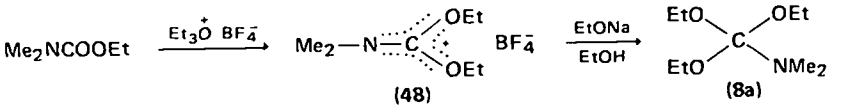


(73)

C. Orthoamides of Carbonic Acid

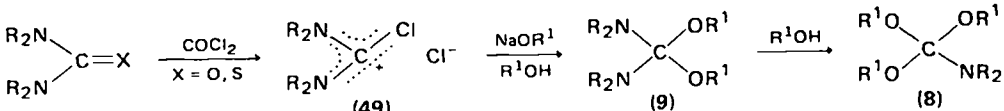
1. Orthocarbamic acid esters

N,N-Dimethylurethan is converted by triethyloxonium fluoroborate into the iminium salt 48 which yields with alcoholic alcoholate the orthocarbamic acid ester 8a[11] (equation 74). Chloroformamidinium chloride (49) which can be prepared by



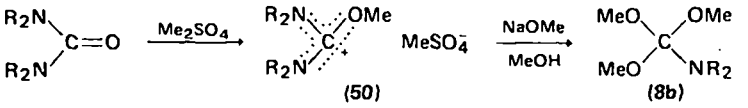
(74)

the action of phosgene on *N,N,N',N'*-tetrasubstituted ureas or thio ureas, is also converted by alcoholic alcoholate into orthocarbamic acid esters 8[67,157] (equation 75). The intermediates are urea acetals 9 which are converted by alcoholysis into



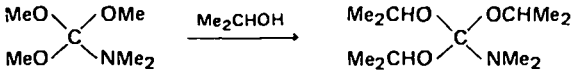
(75)

8[11]. The synthesis of orthocarbamic acid esters 8b from salts 50 which were prepared from urea and dimethyl sulphate[158], proceeds similarly (equation 76).



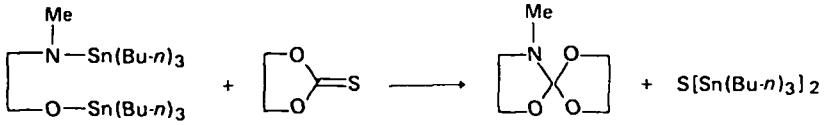
(50) (8b) (76)

Transacetalation, which takes place without addition of acids, can be used to prepare the homologous orthocarbamic acid esters (equation 77)[159].



(77)

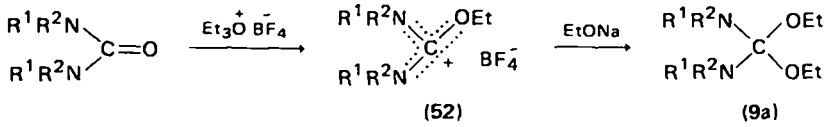
The organotin compound 51 reacts with ethylene thiocarbonate to give the spiro orthocarbamic acid ester 8c (equation 78)[160–162].



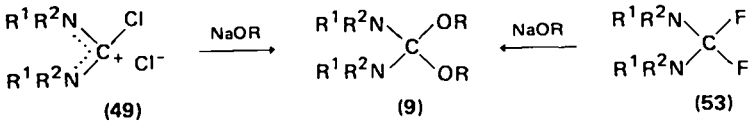
(51) (8c) (78)

2. *Urea acetals*

The most important syntheses of urea acetals 9 are achieved from iminium salts 52[11] and 49[57] as well as from the bis(dialkylamino)difluoromethanes 53[83], on their reaction with alcohol-free alkoxides (equations 79 and 80). Urea acetals 9b

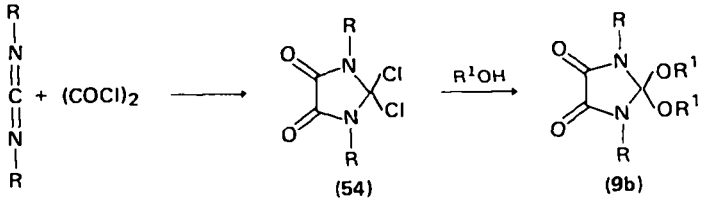


(52) (9a) (79)



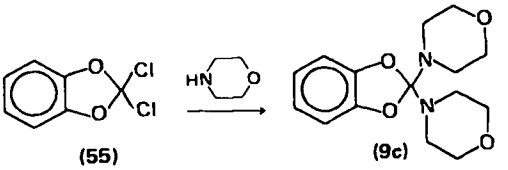
(49) (9) (53) (80)

can be prepared by alcoholysis of the imidozolinedione 54 (equation 81)[163]. The

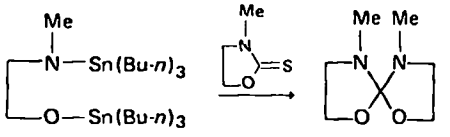


(54) (9b) (81)

aminolysis of catechol dichloromethyl ethers 55 gives the urea acetal 9c (equation 82)[164]. Spirocyclic urea acetals 9d can be prepared from thiocarbamates and organotin compounds 51 (equation 83)[160].



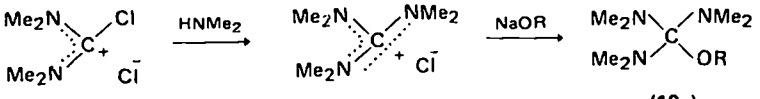
(55) (9c) (82)



(51) (9d) (83)

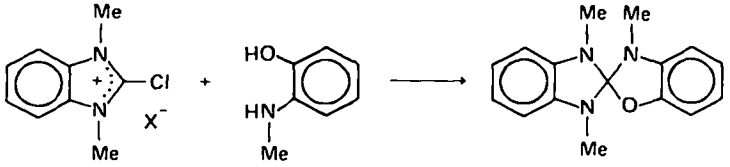
3. *Tris(dialkylamino)alkoxymethanes*

Only one preparative method is known at present for the non-cyclic representatives of this class of compounds. Hexamethylguanidinium chloride, which can be prepared *in situ* from **49a** and dimethylamine, reacts with alcohol-free alkoxides[159,165] to yield tris(dimethylamino)alkoxymethane **10a** (equation 84).



(49a) (10a) (84)

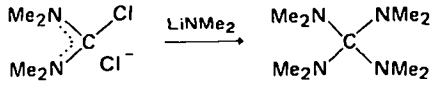
Cyclic compounds of this class, e.g. **10b**, are prepared from 2-chlorobenzimidazolium salts **56** (equation 85)[166].



(56) (10b) (85)

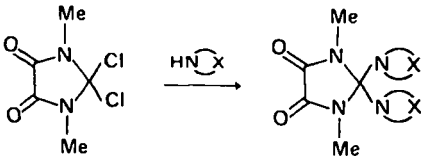
4. *Tetrakis(dialkylamino)methanes*

The simplest member of the series, tetrakis(dimethylamino)methane, may be prepared from **49a** and lithium dimethylamide (equation 86)[167]. Cyclic derivatives

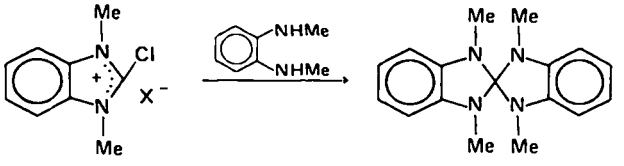


(49a) (86)

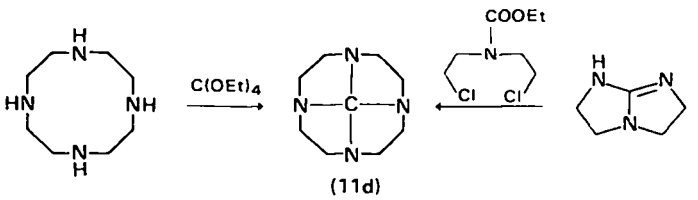
like **11b**[168–170] and **11c**[166] have been obtained from compounds **54a** or **56** (equation 88). Recently the synthesis of the pentacyclic tetrakis-aminomethane **11d** was described (equation 89)[171].



(87)



(88)

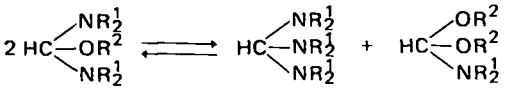


(89)

III. PHYSICAL CHARACTERISTICS AND STRUCTURE OF ORTHOAMIDES

Most of the known orthoamide derivatives are colourless, distillable liquids with an amine-like smell. A summary of the physical characteristics (melting and boiling points) of orthoamides which had been prepared before 1968 can be found in Reference 6.

If moisture is excluded and elevated temperatures are avoided most of the compounds are nearly indefinitely storable, although some of them become coloured yellow or orange. Aminal esters dismutate slowly on standing[108,125] into triaminomethanes and amide acetals (equation 90). The process is catalysed by

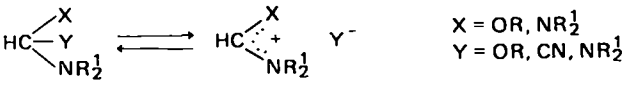


(90)

traces of alcohol. If such a mixture is used as a starting material in syntheses, the product will not be influenced since during the reaction reversal of the dismutation is faster than the dismutation itself. Similar equilibria are also observed with aminal thio esters[48] and mixed-substituted triaminomethanes[129].

Orthoamides, with the exception of tris(acylamino)methanes, are medium to strong bases. Estimates of the basicity based on the strength of hydrogen bonding, i.e. pK values, are for formamide acetals around 7.5[37] and for tris(dialkylamino)methanes about 9.5[3]. Conductivity measurements of formamide acetals[11,108], aminal esters[108] and tris(dialkylamino)methanes[3] as well as of bis(dialkylamino) acetonitriles[172] reveal that orthoamides are weak electrolytes. (The dissociation constants are $10^{-4}-10^{-7}$.)

The electric conductivity of orthoamide solutions generally increases slowly upon standing, pointing to a slow dissociation (equation 91). N.m.r. or i.r. spectro-



(91)

scopy does not furnish proof for the existence of the dissociation product, since it exists only in minute amounts in equilibrium. In some reports the i.r. bands in the region of 1640–1700 cm^{-1} were assigned to the $-\overset{+}{C}=N$ vibration which is in the iminium cation formed by dissociation of the orthoamides. It is likely, however, that this absorption is due to the amide formed by hydrolysis during the preparation of the solutions.

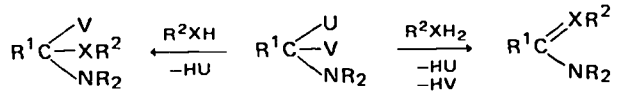
The composition of orthoamides is proven by elemental analysis. Their structure is confirmed by their H-n.m.r. spectra[28,38,43,81,129,145], by the synthetic pathway[16,17] and also by characteristic reactions[10,11], such as hydrolysis, condensation and reactions with Lewis acids. In some hydrolysis experiments thermodynamic parameters were determined, and values were obtained for the enthalpy and entropy of formation as well as for the free energy in the case of dimethylformamide and dimethylacetamide dimethyl acetal[173]. The dipole moment of 2-dimethylamino-1,3-dithiolan was measured[174].

IV. REACTIONS OF ORTHOAMIDES

A. Reactions with Nucleophilic Reagents

1. General considerations

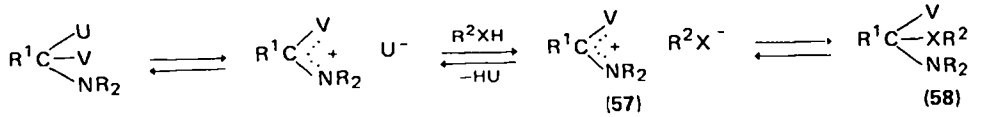
The reactions of orthoamides with nucleophiles can be divided into two main groups. To the first group belong reactions with R^2XH-acidic components, which according to the nature of R^2X lead to another orthoamide or to a product derived from it; to the second group belong reactions with R^2XH_2-acidic components, in which condensation takes place and the orthoamide function is abolished (see equation 92). Both types of reaction have analogous intermediates namely iminium



(92)

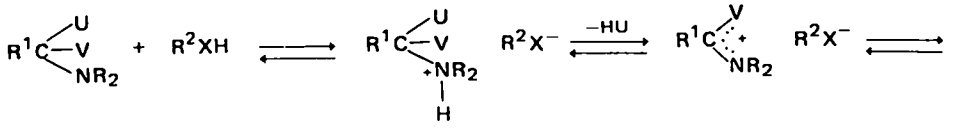
U = OR, SR, NR_2; V = CN, OR, SR, NR_2;
R^2 = H, Alkyl, Aryl, OR, NR_2

salts 57 or adducts 58. Two possibilities for the formation of these intermediates must be discussed[13,175]. In the first, the orthoamide dissociates into an iminium cation and U^-, and U^- deprotonates R^2XH, whereby the iminium salt 57 is formed in equilibrium with the adduct 58 (equation 93). The second possibility is that as a

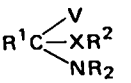


(93)

consequence of their basic characteristics, orthoamides are able to deprotonate R^2XH-acidic compounds, forming salts 59. The latter are stabilized by splitting of HU so that again the same ions 57 or adducts 58 are formed (equation 94). The



(59) (57)

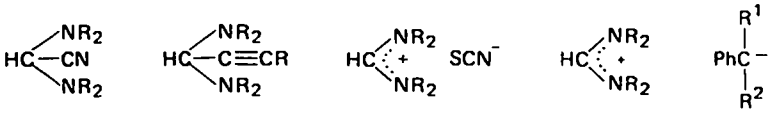


(94)

(58)

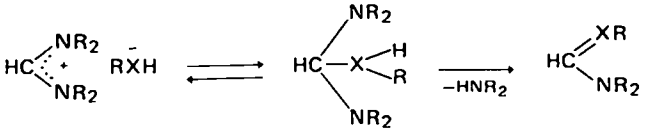
formation of salts **57** or adducts **58** will proceed through one of the above-mentioned paths, depending on the nature of the orthoamide, the acidity of R^2XH and the solvent. In non-polar solvents (for instance toluene) compounds R^2XH with high kinetic and thermodynamic acidity prefer the second route, whereas in polar solvents like DMF, orthoamides which form very stable iminium salts (for example, $V = NR_2$ and $U = SR, OR, NR_2$) yield an adduct with less acidic R^2XH components, according to the first pathway.

The fate of the salts **57** or adducts **58** depends mostly on the nature of the substituents V and on the constitution of the residue R^2 in R^2X^-. In the case of $V = NR_2$, strong $R^2X^{(-)}$ nucleophiles (for example CN, —C≡C—R) yield stable adducts[116,148] (for instance **13a**, **60**). When R^2X^- is less nucleophilic, resonance-stabilized anions like SCN^- [176] or carbanions of the type $Ph—CR^1R^2$ form stable amidinium salts **61** and **62**. The use of drastic reaction conditions in these cases may lead to secondary reactions, for instance amidation of the ester function[116].



(13a) (60) (61) (R^1, R^2 = CN, COOR) (62)

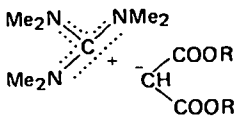
If in the above-mentioned case ($V = NR_2$) the RXH_2-acidic compounds are brought into reaction, the same considerations are valid. However, there exists a possibility of a further irreversible reaction to form the condensation product **63** by splitting off a dialkylamine (equation 95). This reaction is always observed in the case of tris(alkylamino)methanes, aminal esters and aminal thio esters as well as with their vinylogues[177].



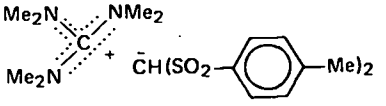
(95)

(63)

With orthoamides of carbonic acid some cases are known where the reaction with RXH_2-acidic compounds stops at the stage of iminium salts[159,178] (also with carbanions of medium stability), see for instance **64** and **65**. When in **57** V is OR or

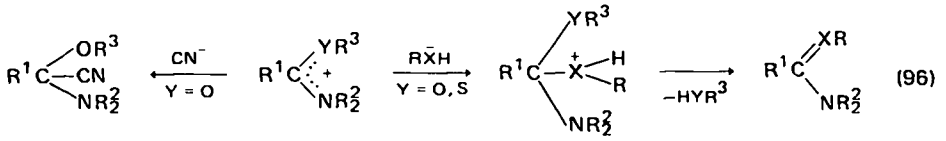


(64)



(65)

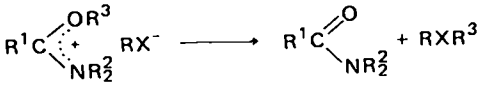
SR these are typical ambivalent cations 57a, for which the reaction principles derived by Hunig are valid[59]. Accordingly strong nucleophilic anions RX^-, for example, add to yield the isolable adduct 12. In the case of RXH_2 acidic com-



(96)

(12) (57a) (63)

pounds, an alcohol or a thiol is split off yielding the condensation product 63. On the other hand, when the anions are well stabilized by resonance and are less nucleophilic, or when the residue R^1 is bulky and interferes with the addition of RX^- or RXH^-, the anions attack the polarized $Y-R^3$ bond at the periphery of the iminium salt 57a (equation 97). By these nucleophilic substitutions the thermo-



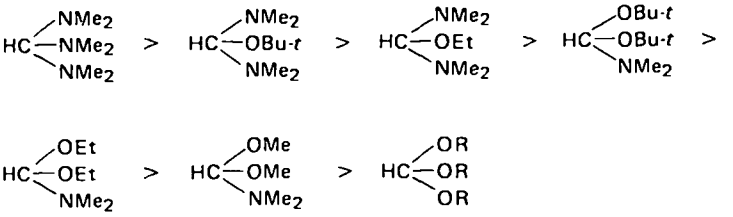
(97)

(57a)

dynamically stable products are formed. Such reactions were observed, for example, as parallel reactions in the condensation of lactam acetals with CH_2 acidic compounds, as well as in the exchange reaction of formamide acetals with tertiary CH acidic compounds.

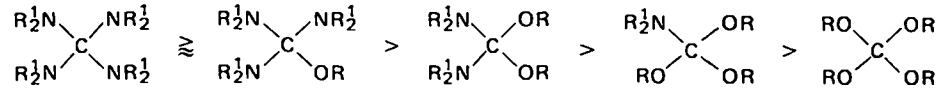
Compared to orthoesters, orthoamides show enhanced reactivity. This is attributed on the one hand to their higher basicity (which facilitates the anion formation from the substrate) and on the other to the higher stability of iminium ions in comparison to carboxonium ions.

In the series of carbonic acid orthoamides there exists a clear gradation of reactivity towards weak RXH_2 acidic compounds, which is based on the stability of the iminium ions formed during the reaction. Comparative investigations in the series of orthoformic acid derivatives established the following reactivity series[38,108,175,179]:



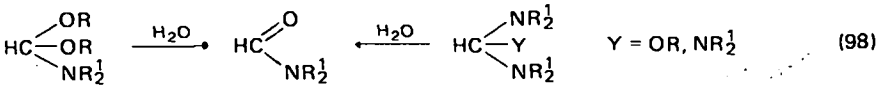
The thio analogues show lower reactivity[43] as do amide acetals with electron-withdrawing substituents in the α-position of the orthoamide function[13]. In the

series of orthocarbonic acid derivatives, when the number of dialkylamino groups in the molecule was increased, the following increase in reactivity was observed[8,159,165,188]:



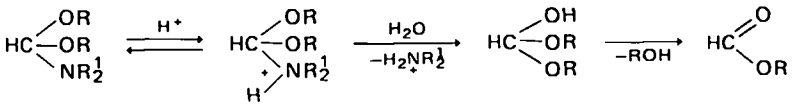
2. *Reactions with compounds containing hydroxyl groups*

a. Hydrolysis. *N*-Alkyl- and *N*-aryl-substituted orthoamides undergo unusually easy hydrolysis in neutral, acidic or basic media to yield amides (equation 98)[11,76,173,180,181]. The sensitivity towards hydrolysis declines according to the series given in Section IV.A.1.



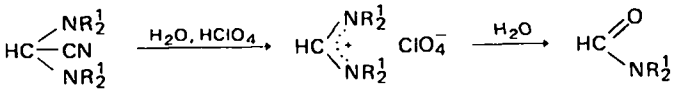
(98)

During the hydrolysis of amide acetals in acidic media, some ester is formed due to the competitive reaction (99)[11,173,181].



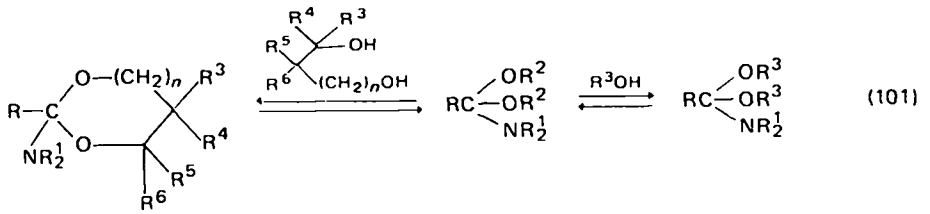
(99)

In some instances of acid hydrolysis of aminal esters and tris(dialkylamino)methanes, amidinium salts were proven as intermediates[145,182]. Cyclic amide acetals[11,183–185] and orthocarbamic acid esters[11,157] are more stable towards hydrolysis than the corresponding non-cyclic representatives. An exception is 2-dialkylaminobenzo-1,3-di-oxole[76]. Quite stable towards hydrolysis are dialkylaminoalkoxy and bis(dialkylamino) nitriles 12 and 13, which can even be prepared in aqueous solution[42,64]. The hydrolysis of bis(dialkylamino) acetonitriles in acidic medium leads, after expulsion of HCN, to amidinium salts 31a, which can be isolated or converted subsequently to *N*-formylamines (equation 100)[148,150].



(100)

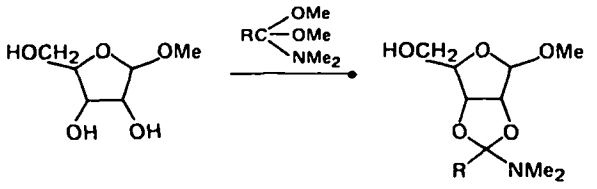
b. Alcoholysis. Amide acetals undergo transacetalation by higher alcohols without a catalyst (equation 101), but mixed amide acetals cannot be prepared by



(101)

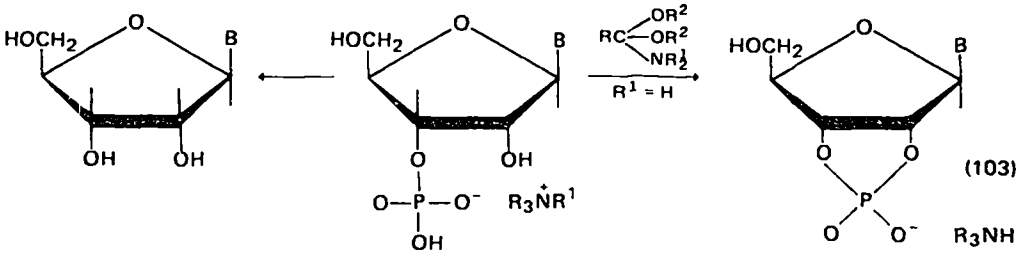
this procedure[11,26,28,38,109]. Glycols yield 2-dialkylamino-1,3-dioxanes or -dioxolanes (compare Section II.A.6).

Cis vicinal hydroxyl groups of sugars can be protected by formation of the amide acetal function (equation 102)[183-185]. Amide acetals cause the cyclization



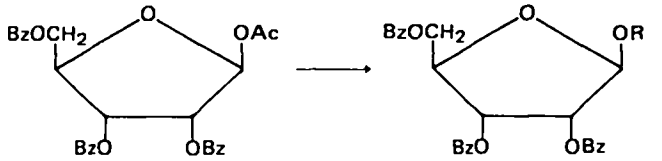
(102)

of ammonium ribonucleoside-2',3-phosphate[186,187] whereas tetraalkylammonium phosphate undergoes dephosphorylation[187] (equation 103). Cyclic and non-cyclic



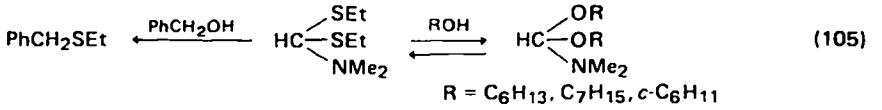
(103)

amide acetals can be used for the glycosidation of protected acylated sugars (equation 104)[188,189].



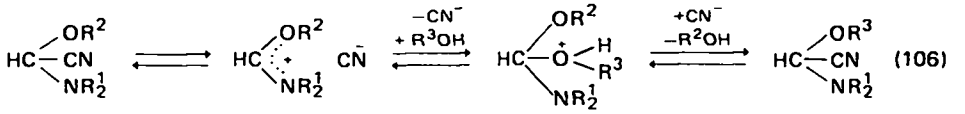
(104)

Thio acetals can be transacetalated with alcohols to *O,O*-acetals (equation 105). Because of the higher nucleophilicity of thiols, forcing conditions have to be



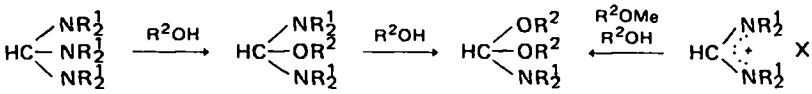
(105)

applied so that the thermodynamically controlled formation of thio ethers can compete[44]. Dialkylaminoalkoxy acetonitriles can also be transacetalated according to the equilibrium process (106)[149].



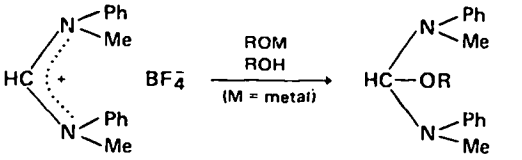
(106)

Tris(dialkylamino)methanes react with alcohols to yield aminal esters, which then react with excess alcohol to give amide acetals (equation 107)[28,108]. This reaction has preparative significance for the synthesis of amide acetals with bulky alkoxy groups. In this case the aminal esters are produced *in situ* from tetra-



(107)

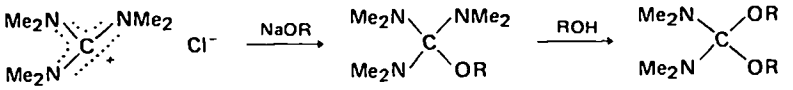
substituted formamidinium salts such as the chloride[38] or the methyl sulphate[60] or alternatively from 1,1-bis(dialkylamino) acetonitriles[42] and an alcoholic alcoholate. *N*-Alkyl-*N*-aryl-substituted aminal esters seem to undergo alcoholysis much less easily than the *N,N*-dialkyl-substituted analogues, since some of the former can be prepared in high yields from alcoholic alcoholate and the formamidinium salt **316** (equation 108)[88].



(108)

R = Me_2CH, Me_3C

Among carbonic acid orthoamides a clean transacetalation is only possible with orthocarbamic acid esters[158,190]. Urea acetals yield by alcoholysis orthocarbamic acid esters[11,57,157,159] (compare Section II.C.1). In the synthesis of tris(dimethylamino)alkoxymethanes **10a**, from hexamethyl guanidinium chloride, which was prepared *in situ*, the urea acetals are obtained as alcoholysis products (equation 109)[165].

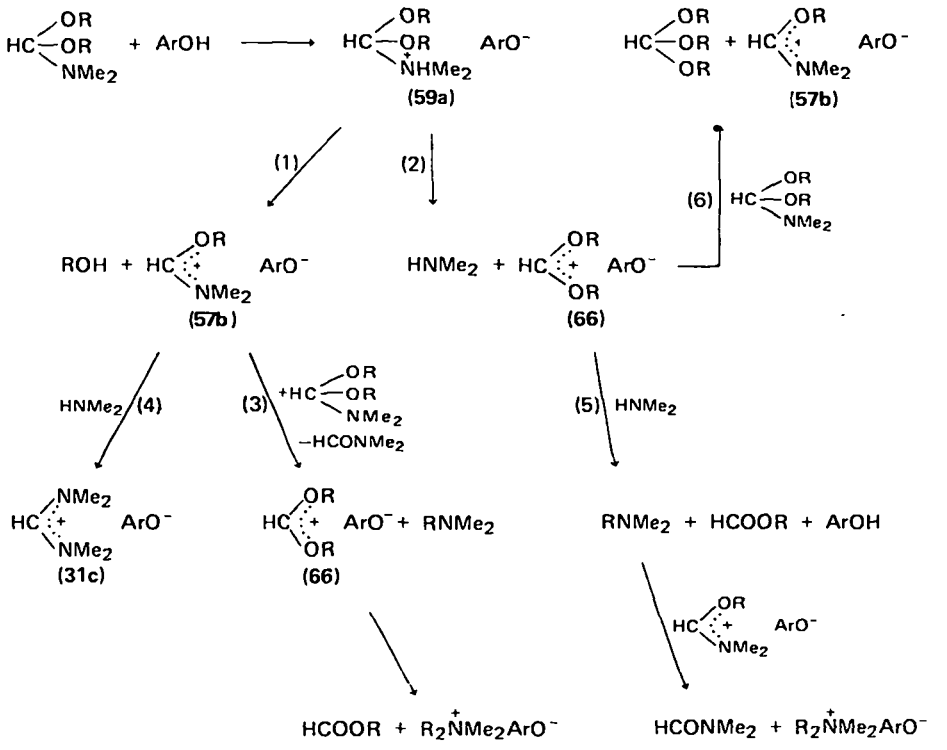


(109)

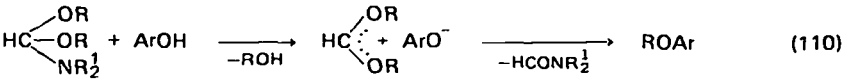
See also Section VII.

c. Reactions with phenols. The nature of the products obtained by the action of phenols on orthoamides is influenced to a large extent by the acidity of the phenols. Strongly acidic phenols ($pK_a < 3$) transform amide acetals into a mixture of tetralkylammonium and *N,N,N',N'*-tetraalkylformamidinium salts. Orthoesters and amides are also formed[180,191]. The formation of carboxonium ions **66** and iminium ions **57b** (which are also formed in the reaction of amide acetals with HCl[11] are assumed to be significant in the formation of these reaction products, which are obtained through a series of complex reactions. The carboxonium ions and iminium ions are formed mainly by decomposition of the *N*-protonated amide acetals **59a** (pathways 1 and 2 in Scheme 1). Carbonium ions (**66**) as well as iminium ions **57b**[192,193] are very good alkylating agents and react with amide acetals similarly to methyl iodide[11], giving, for example, carboxonium ions **66** and tertiary amines (pathway 3). Amine that was formed according to (2) then reacts partly in the usual way with the iminium salt **57b** to yield the amidinium salt **31c** (pathway 4). Carboxonium ions **66** which were formed according to (2) and (3), are able to react with amide acetals by alkoxide transfer[10,11] to give orthoesters and alkoxymethylene iminium salts **57b**. The latter participates again in the reaction (6). The ions **57b** and **66** may also quaternarize the tertiary amine formed according to pathways (3) and (5).

Less acidic phenols react with amide acetals to yield phenyl ethers (equation 110)[180,194,195]. Transacetalations are not observed in these cases. Phenols with

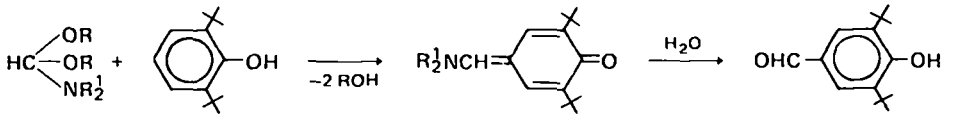


SCHEME 1



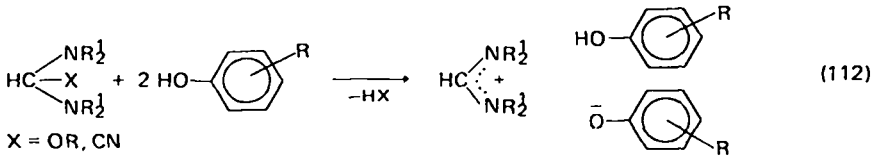
(110)

bulky groups in the 2,6-positions undergo formylation in the aromatic nucleus (equation 111)[191]. Aminal esters[172,191] as well as bis(dialkylamino) aceto-



(111)

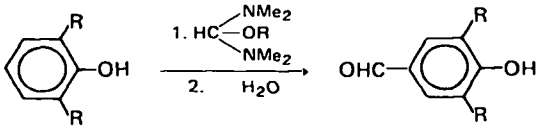
nitriles[172] react with phenols to give amidinium salts (**31d**) with a complex phenol/phenolate anion (equation 112). Reactive phenols, such as 2,6-dialkyl-



(112)

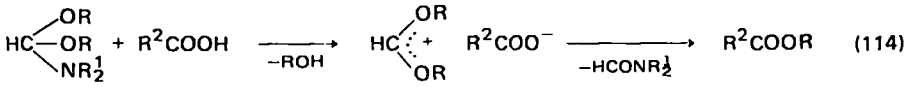
(**31d**)

phenols or β-naphthol under forced conditions, undergo formylation by aminal esters, on the aromatic nucleus (equation 113)[191].



(113)

d. Reactions with carboxylic acids. Carboxylic acids are esterified by amide acetals (equation 114)[26,109,180,194-198]. Aliphatic dicarboxylic acid[194,195],

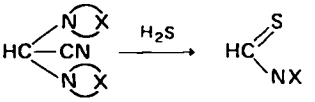


(114)

aromatic (also sterically hindered)[26,194,195] and heterocyclic acids as well as amino acids[26,109,198] and peptides are accessible for this reaction. As by-products ammonium salts[180,195] are formed. The best yields are obtained when working with dilute amide acetals, in solvents like benzene or chlorinated hydrocarbons and at low temperatures[195]. Especially suitable for the preparation of methyl esters is 1,1-dimethoxypyrrolidino methane[195]. The esterification proceeds by alkylation of the acid anions through a S_N2-mechanism[26].

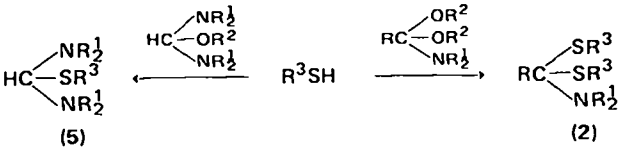
3. Reactions with compounds containing acidic SH groups

The thiolysis of orthoamides had scarcely been investigated until recently. However, formation of *N,N*-disubstituted thioamides is assumed as was observed in the thiolysis of α,α-bis(dialkylamino) acetonitriles (equation 115)[148,199]. Thiols



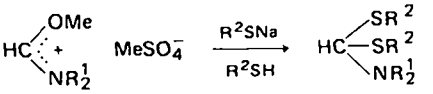
(115)

react with amide acetals[43,44,110-113] or aminal esters[43] to yield amide thioacetals 2 or aminal thioesters 5 (equation 116). The preparation of amide thioacetals from



(116)

alkoxymethylene iminium salts and alkali thiolates in excess of thiol is also based on this transacetalation reaction (equation 117)[5,43,44]. However, mixed *O,S*-acetals cannot be prepared in this manner[43].

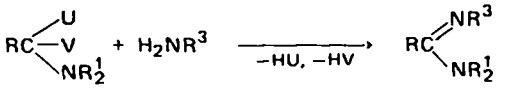


(117)

4. Reactions with compounds containing acidic NH_2 or NH groups

a. Compounds containing acidic NH_2 groups. Compounds containing acidic NH_2 groups condense with orthoamides, according to the mechanism formulated in

Section IV.A.1, to yield amidines (67) (equation 118). The following compounds have been used in this reaction: amide acetals[11,13,38,85,86,183,184,200–211], amide thioacetals[44,46], aminal esters[212–214], triaminomethanes[128,215], lactam acetals[216–221], alkoxydialkylamino acetonitriles[149] and bis(dialkylamino) acetonitriles[148,199]. The condensations with vinylogous orthoamides which are frequently prepared *in situ* proceed similarly (for a summary see Reference 222).



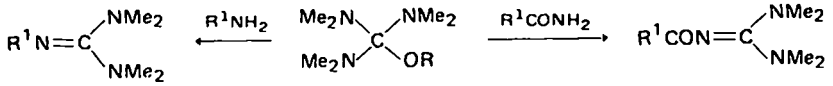
(118)

(67)

The following compounds were used, among others, as acidic NH_2 components: aliphatic amines[149,214,221], aromatic amines[11,85,128,148,149,200,201,215,217–219], alkylhydrazines[85,149], arylhydrazines[11,85,215,221], *N*-acylated amines like primary amides[85,212,213] and thio amides[208,209], ureas and thio ureas[85,201,215], guanidines[200,204], amidinium salts[86], amidines[207], semicarbazides[11] and sulphonamides[85]. Furthermore, the condensation also succeeds with primary hetrocyclic amines like aminopyrimidines[183,184,202,205], aminopyridines[200–202,205,206] aminopurines[183,184,210], aminothiazoles[202], amino-1,2,4-triazoles[183,184], amino-*S*-triazines[183–184,205,206], amino-1,2,3,4-tetrazoles[183,184], amino-1,3,4-oxadiazoles[203], aminopyridazines[205], aminopyrazines[205], aminopyridazine-*N*-oxides[206], aminopyridinium salts[206] and aminopyridazinium salts[206].

This summary indicates that the reaction of compounds containing acidic NH_2 groups with orthoamides is probably the most general method for the preparation of amidines and amidrazones. This procedure is also important in the nucleoside field for the blocking of amino functions[183,184]. If besides the amino group other functional groups are also present, which are able to react either with the orthoamide or with the formed amidine, secondary reactions such as formation of cyclic amide acetals may occur together with the formation of amidines, as in the reaction of nucleosides with amide acetals[183,184]. Cyclization to heterocyclic[207,217,223,224] compounds may occur when bifunctional components like *o*-aminophenols, *o*-aminothiophenols and *o*-phenylenediamine are used. Furthermore, the nitrogen of heterocyclic rings may be alkylated under certain circumstances (cf. Section IV.A.4.b).

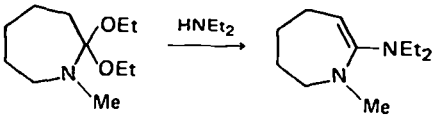
In the orthocarbonic acid series the only reactions known are those of tris(dimethylamino)alkoxymethanes with compounds containing acidic NH_2 groups (equation 119)[8,159,165]. Primary amides (formamide and higher homologues), as well as oxamide, react to give *N*-acylguanidines[8,159]. Malondiamide, on the other hand, reacts at the CH_2 group[8,165]. Aliphatic amines yield *N*-alkylguanidines[159].



(119)

See also Section VII.

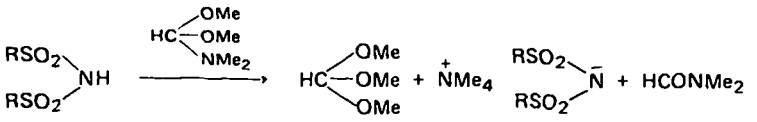
b. Compounds containing acidic NH groups. Reactions with secondary amines or imides, which again yield orthoamides are described in Section II.A.6 and II.B.6. Seven-membered ring lactam acetals react with aliphatic amines to yield ketene aminals 68 (equation 120)[221].



(120)

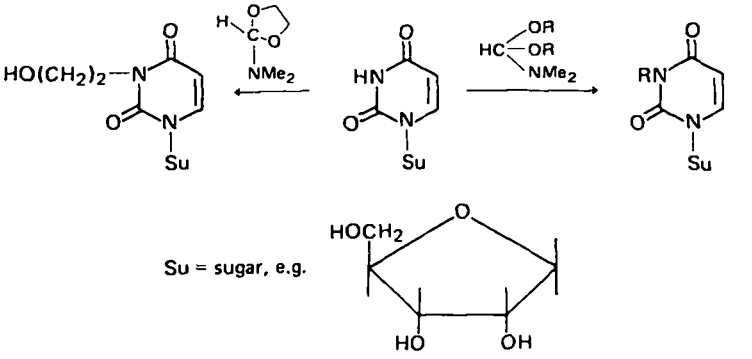
(68)

The reactions with compounds containing strongly acidic NH groups like carbonic acid imides or disulphonylamines are similar to those with phenols or inorganic acids and the products are orthoesters, ammonium salts and amides (equation 121)[127,180]. The reactions can be formulated analogously (cf. Section IV.A.2.C).



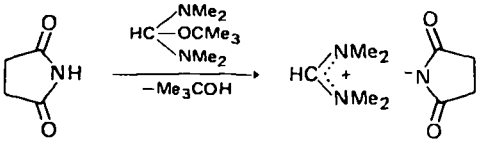
(121)

Compounds containing weakly acidic NH groups undergo alkylation by amide acetals at the nitrogen atom (equation 122)[196,225-231]. This exceptionally selec-



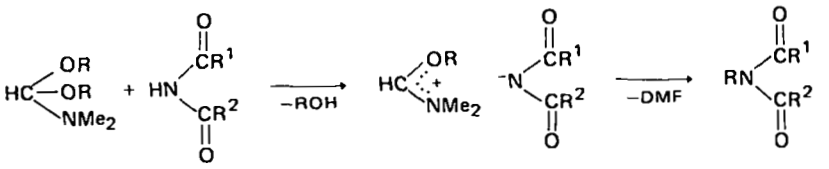
(122)

tive reaction was used until recently with nucleosides and substituted or annellated dioxopyrimidines. The introduction of 2-hydroxyethyl groups can be accomplished using 2-dimethylaminodioxolane[196,231]. Formamidinium salts are formed from aminal esters and imides (equation 123)[127]. It may therefore be assumed that the

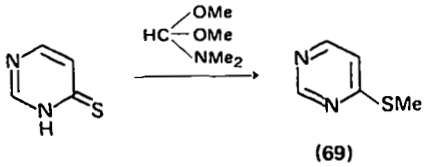


(123)

reaction of compounds having weakly acidic NH groups with amide acetals takes place through a nucleophilic substitution of the alkyl residue on the alkoxymethylene iminium salt (equation 124)[226]. Exceptions are the thio analogues of compounds having acidic NH groups, as for example **69** which is alkylated on the sulphur (equation 125)[232].



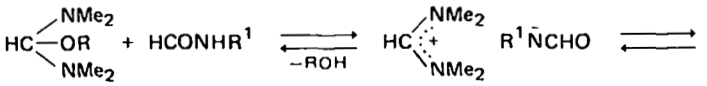
(124)



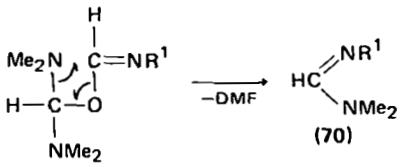
(125)

(69)

The reaction of *N*-monosubstituted formamides with aminal esters is the basis for a useful synthesis of *N,N,N*-trisubstituted formamidines (70) for which the mechanism shown in equation (126) may be considered[233].



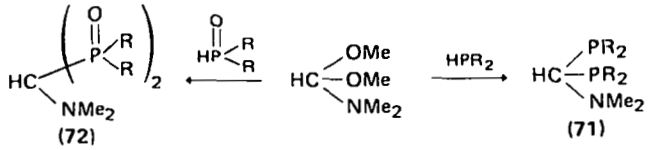
(126)



(70)

5. *Reactions with compounds containing acidic PH groups*

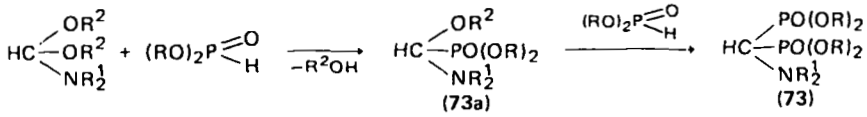
Dimethylformamide dimethylacetal reacts with secondary phosphines or dialkylphosphine oxides to yield dimethylamino diorganophosphinomethanes (71)[234] or dimethylamino bis(dialkylphosphinyl)methanes (72) (equation 127)[235]. Similarly,



(127)

(72) (71)

amide acetals and phosphoric acid esters give *N,N*-dialkylaminomethane phosphonic esters 73 (equation 128)[5,235-239]. Under delicate conditions one can isolate the

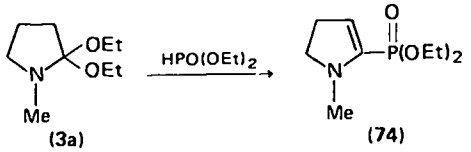


(128)

(73a) (73)

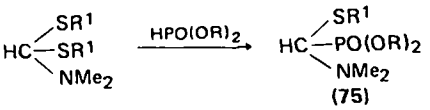
intermediary dialkylaminoalkoxymethane phosphonic esters 73a[5,235] Cyclic amide acetals and cyclic phosphoric acid esters cannot be used in this reaction[235].

The lactam acetal **3a** reacts with diethyl phosphite to yield the phosphonic ester (74) (equation 129)[240]. Dimethylformamide thioacetals and phosphoric



(3a) (74) (129)

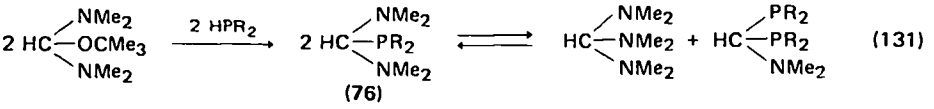
esters form dimethylaminoalkylthiomethyl phosphonic esters (75) (equation 130)[235]. Aminal esters and dialkylphospines yield bis(dimethylamino)dialkyl-



(75) (130)

phosphinomethanes (76) which undergo slow disproportionation (equation 131)[241].

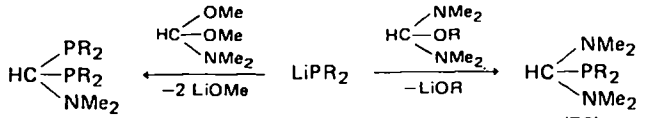
See also Section VII.



(76) (131)

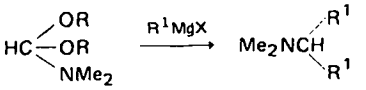
6. Reactions with organometallic compounds

Substitution reactions of orthoamides succeed only with strong nucleophiles because of the weak nucleofugacity of the leaving groups. Thus lithium dialkylphosphides react with dimethylformamide acetal to give bis(dialkylphosphine) dimethylaminomethanes (71)[234] or with the aminal ester **4** to give bis(dimethylamino)dialkylphosphinomethanes 76 (equation 132)[241].



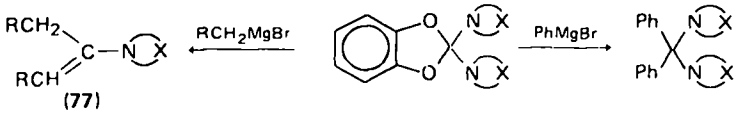
(71) (76) (132)

Grignard reagents react with dimethylformamide acetals to yield tertiary amines (equation 133)[5,207,242]. 2,2-Bis(dialkylamino)-1,3-benzdioxoles with Grignard



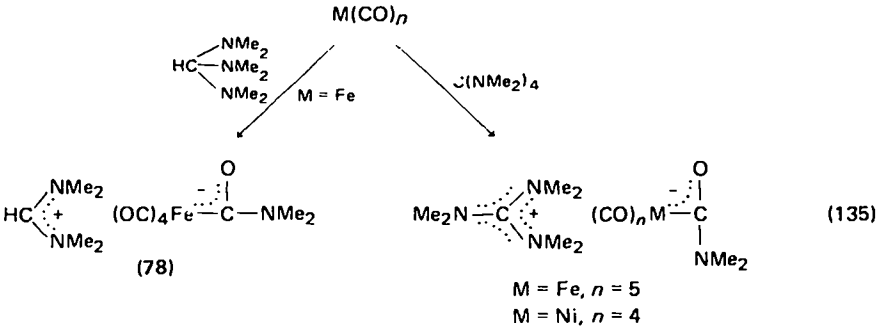
R^1 = Et, Ph, C_6H_4X (X = *p*-MeO, *o*-MeO, *p*-Me, *m*-Me, *o*-Me) (133)

reagents give aminals; when α-CH bonds are available enamines (77) are produced (equation 134)[243].



(77) (134)

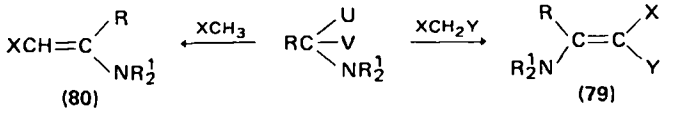
Tris(dimethylamino)methane reacts with iron pentacarbonyl to yield a carbomoyl–tetracarbonyliron complex salt (78)[244]. Analogous reactions occur with tetrakis(dimethylamino)methane and nickel tetracarbonyl or iron pentacarbonyl[245] (equation 135).



(135)

7. Reactions with carbon acids

a. Compounds containing acidic CH_2 groups. Orthoamides condense with carbon acids of the type $X-CH_2-Y$ or $X-CH_3$ to yield the enamines 79 and 80 (equation 136). The reaction conditions depend on the acidity of the carbon acid.

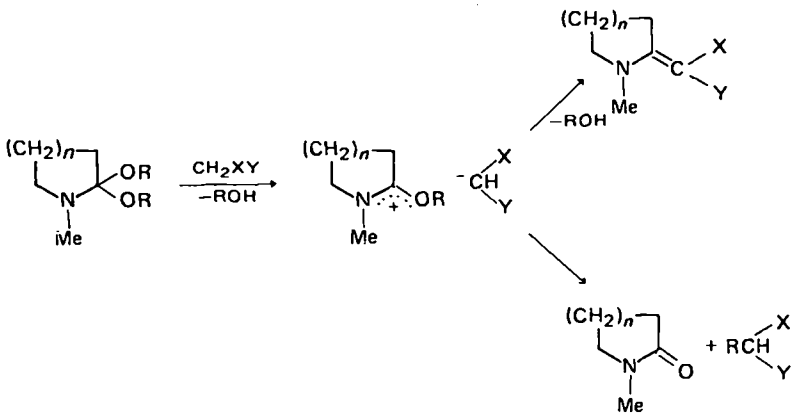


(136)

Stronger CH-acidic compounds, as for instance cyanoacetic esters, react even at room temperature, whereas with weaker carbon acids it is necessary to heat the mixtures prolongedly at 160°C, with simultaneous distillation of the volatile components. Of special significance are the orthoamides of formic acid, because the formed enamines can be used as potential aldehydes for an exceptionally broad area of further reactions, such as heterocyclic syntheses (cf. Section IV.A.8.b).

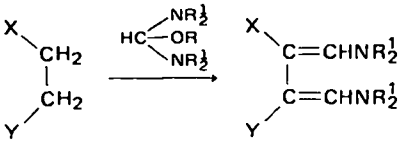
Among these condensations, various dimethylformamide acetals[11,25,26,38,175,179,240,246-269] were reacted with nitroalkanes[11,246-248,264], cyanoacetic acid derivatives[11,26,179,249,265], 1,3-dicarbonyl compounds[11,38,250,251], ketones[11,38,179,252,253,256,257,266,267], 1-methyl-2,2(dialkoxycarbonyl)ethylenes[25], α-cyanocrotonic esters[263], alkyliminium salts[268]; alkylpyrimidines[175,269], cyclopentadiene[11], nitroalkylimidazoles[255], nitrotoluenes[258,259,262], 5-alkyl-1,2-dithiolthiones[261], phosphonium salts[260] and 1,3,4-thiadiazolium salts[254]. Dimethylacetamide acetals[11,242,248,264] and higher homologues[248,264], amide acetals containing functional groups α to the orthoamide groups[13] as well as bis-amide acetals derived from dicarboxylic acids[13] were condensed with nitroalkanes[11,13,242,248,264], derivatives of cyanoacetic esters[11,242], nitrotoluenes[11,242] and cyclopentadiene[11,242]. Such condensations were also performed on a series of lactam acetals[11,216,221,242,265,270-275]. In this case alkylation of the acidic CH bond was also observed as a parallel reaction (equation 137)[221,231].

As a result of their extreme reactivity, aminal esters[127,175,179,212,233,249,253,260,276-278] and triaminomethanes[128,178,215] react with strong as well as weak carbon acids to yield enamines. The following compounds containing acidic



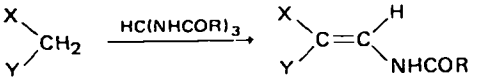
(137)

CH_2 groups were found to undergo formylation: cyanoacetic ester derivatives[179,249], alkylnitriles as well as α-monofunctional nitriles[128,215,233,249,276], aliphatic ketones[128,179,215,276], alicyclic ketones[277], carboxylic acid esters[212,233,276], lactones[212], carboxylic acid thiol and thion esters[212], imino carboxylic acid esters[233], alkyloxazolines[233], isonitriles[233], amides[212], *N*-alkylimides[127], thio amides[212,254], amidines[233], phosphonium salts[278], phosphonic acid esters[233,260], substituted toluenes[128,175,215,253], substituted heterocyclic compounds like alkylpyridines[128,175,215], quinolines, acridines, benzoxazolines and benzimidazolines[175], 2,5-dialkyl-1,3,4-thiadiazoles[254], 2,4-dialkyl-1,3-dithiadiazepines(5,6)[254], flourene[178] and xanthene[178]. In some cases it was possible to formylate acidic geminal CH_2 groups (equation 138)[127].



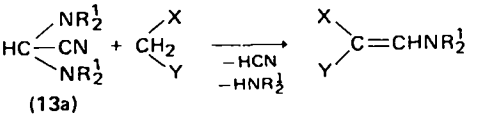
(138)

Tris(acylamino)methanes react with cyanoacetic and malonic esters[279] and ketones[139] to give *N*-acyl enamines in low yields (equation 139). Amide thio-



(139)

acetals[43,44,46] and aminal thioesters[43] have also been used in similar condensations. Vinylogous orthoamides also react with carbon acids[177,280] (for a summary see Reference 222). Condensation of bis(dialkylamino) acetonitriles 13a with compounds containing acidic CH_2 groups is also possible; however the workup of the reaction product is difficult because the hydrocyanic acid formed polymerizes during the reaction (equation 140)[172].

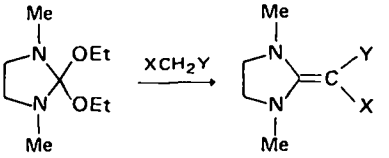


(13a)

(140)

Only a few reactions of orthoamides of carbonic acid with compounds containing acidic CH_2 groups have been described[8]. Orthocarbamic acid esters react relatively slowly and can be brought to reaction only with strongly acidic methylene components such as cyanoacetic ester, malononitrile[11,159], rhodanines[11] and imidazolones[11]. In some cases alkylation of carbon acids has been observed as well as condensation[159].

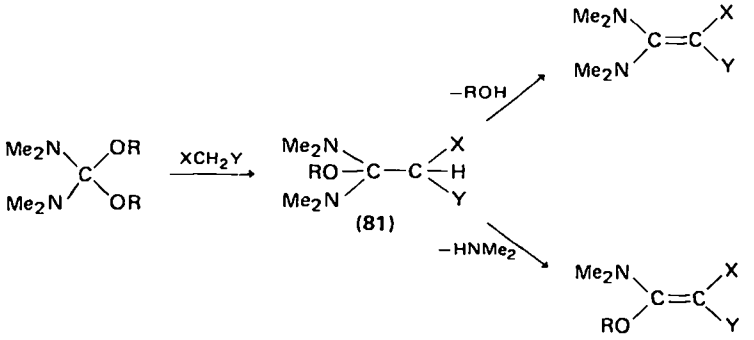
Even though urea acetals are more reactive than orthocarbamic acid esters, only acetals with nitrogen bridges (9e) are suitable for such condensations (equation 141)[11], since with non-cyclic compounds, the primarily formed adduct 81 may



(141)

(9e)

split off either alcohols or amines, resulting in a mixture of ketene *O,N*- and ketene *N,N*-acetals (equation 142)[8,11,159]. Moreover, the alcohol may also react with urea acetal to yield the less reactive orthocarbamic ester[11].

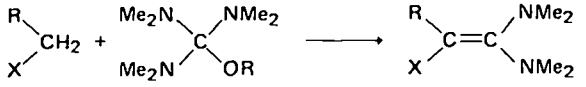


(142)

(81)

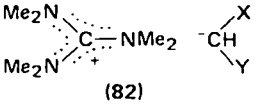
On the other hand, the condensation of tris(dimethylamino)alkoxymethanes[159,165] or tetrakis(dimethylamino)methanes[178] with carbon acids is quite impressive, and leads to the formation of ketene aminals[8] which are otherwise hardly accessible. It is possible to obtain from alkylnitriles[159], α-functionalized nitriles[159], carboxylic acid esters and amides[165] and fluorene[178] the corresponding ketene aminals (equation 143). With carbon acids forming stable anions the reaction sometimes stops at the stage of guanidinium salts (82)[159,178].

See also Section VII.



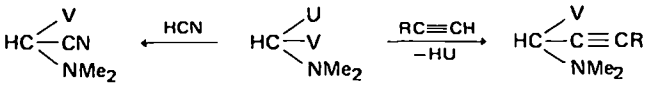
(143)

X = CN; R = H, Me, Et, Pr, OMe, NMe_2, CN, COOMe
X = COOMe; R = Me
X = $CONMe_2$; R = H, Me



(82)

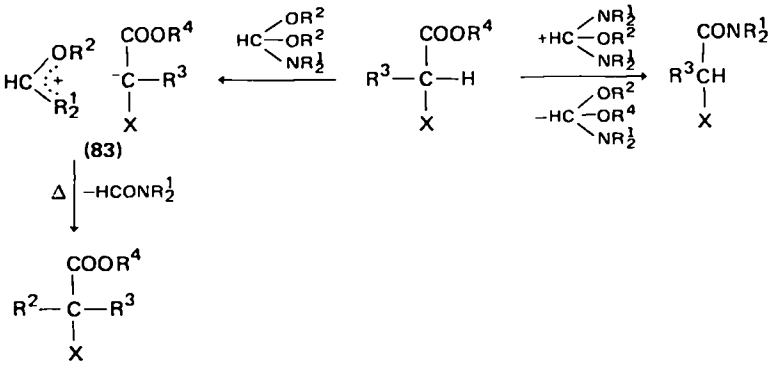
b. Acidic methine groups. Of preparative significance are reactions of orthoamides with acetylene and hydrocyanic acid, in which *O,N*-acetals or -aminals of propargyl aldehydes[67,281] or acyl cyanides[84,115,116] are formed (equation 144).



(144)

U = OR; V = NMe_2, OR

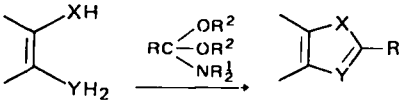
Very strong carbon acids form in the first step a salt, for example 83, and the reaction stops under mild conditions at this stage[116]. Under forcing conditions, however, alkylation of the carbanion occurs with amide acetals[116], whereas aminal esters or triaminomethanes produce amidation of the ester function.



(145)

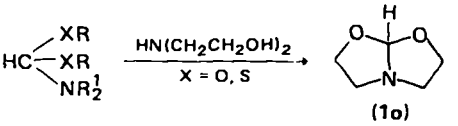
8. *Heterocyclic syntheses using orthoamides*

a. Cyclization of oligofunctional components. Difunctional compounds like diamines[207,223], amino alcohols[149,207], amino sulphonamides[207], amino amides[207] amino thiols[223], hydroxy ketones[252,256,257,267] and nitroso amines[224], where the two functions are adjacent, for instance in the *ortho* positions of benzene rings or heterocyclic systems, can be cyclized with amide acetals and other orthoamides (equation 146). According to this scheme the



(146)

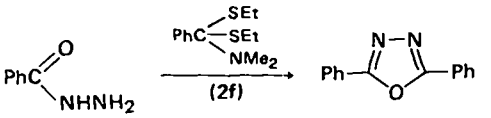
following compounds were prepared: chromones[252,256,257,267], aminopurines[224], pyrrolo[1,2-*a*]quinolines[262], benzoxazoles[149,207], benzimidazoles[207,223], quinazolones[207], benzothiadiazine-1,1-dioxides[207], *peri*-naphthodihydropyrimidine[207], benzthiazoles[223], thiazolo[5,4-*b*]pyridine[223], imidazo[4,5-*b*]pyridine[223], imidazo[4,5-*c*]pyridine[223], pyrido[3,2-*d*]pyrimidine-4(3*H*)-one[223] pyrido[2,3-*d*]pyrimidine-4(3*H*)-one[223] and 1,3,4-oxathiazole-3,3-dioxides[282]. Diethanolamine reacts, both by transacetalation and by transamination, with dimethylformamide acetal[38] as well as thioacetal[44] to yield the bicyclic amide acetal 1o (equation 147). Benzhydrazide undergoes cyclization under the



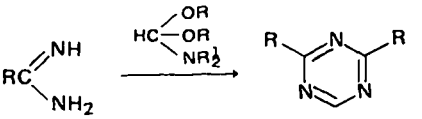
(1o) (147)

influence of thio acetal 2f to 1,2,4-oxadiazole (equation 148). Guanidines, amidines, isoureas and isothioureas react with amide acetals to give 2,4-disubstituted *s*-triazines[200,201,283,284] or triazionones[284] (equation 149).

See also Section VII.

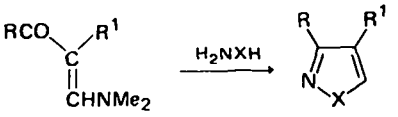


(148)

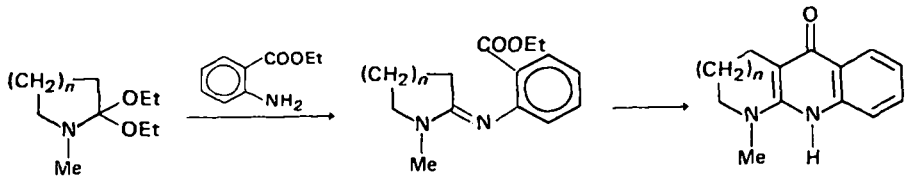


(149)

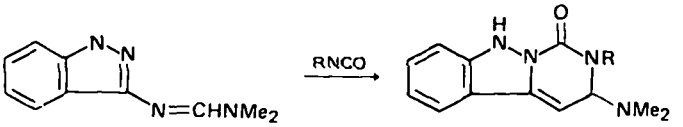
b. From condensation products of orthoamides with compounds containing acidic NH_2 and CH_2 groups. The formation of enamines or amidines by reaction of orthoamides with compounds containing acidic NH_2 and CH_2 groups is used in the synthesis of various heterocyclic compounds. The condensation products are often not isolated but directly cyclized with other starting materials. Some informative examples are summarized in equations (150)–(153). According to these and



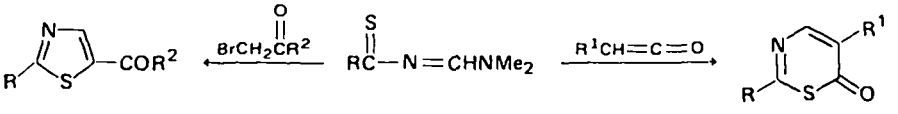
(Refs 276, 289, 290, 291) (150)



(Refs 35, 217, 274) (151)



(Ref. 294) (152)

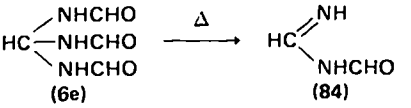


(Refs 208, 209) (153)

similar procedures the following types of compounds have been prepared: indoles[258,285-288], pyridines and their derivatives[25,251,253,263], pyrazoles and isoxazoles[276,289-291], pyrimidines[246,249,276,289,290], purines[292,293], *s*-triazines[200,201,249,283], heterocyclic annelated 1,3,5-triazoles[205,211], 6-oxo- or 6-thioxo-6*H*-1,3-thiazines[208,209] thiazoles[208,209], pyrroloquinolones[35,217,274], quinazolones[35], indazoles[294], pyridazines[211], 2*H*-furanone-(3)[313] and uracils[265].

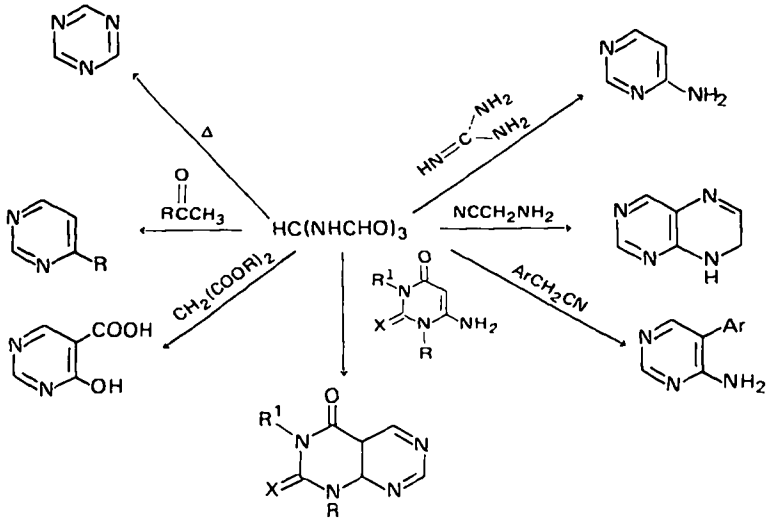
See also Section VII.

c. Synthesis of heterocyclic compounds using tris(acylamino)methanes. Tris(acylamino)methanes and especially tris(formylamino)methane were found to be exceptionally useful and versatile starting materials for heterocyclic syntheses[133,285]. As the intermediate in these syntheses, formylformamidin 84 was proposed, assumed to be formed during the thermolysis of 6e[295], and able,



(6e) (84) (154)

according to the substrate to provide C_1, –C=N or –C=N–C– fragments. 6e reacts with hydrazines[296], α-hydroxy or α-halogeno ketones[133], guanidines[133,200,201,284,296,297], ureas[200,201,297], ketones[133,279,298-302], aryl acetonitriles[303,304], aryl acetamides[304], malonic and cyanoacetic ester derivatives[279,305], amino acetonitriles[217,303,306], 4-aminouracils or 3-aminopyrazolones[307-309] and β-aminovinyl carbonyl compounds, yielding 1,2,4-triazoles[296], oxazoles[133], monoamino-*s*-triazines[133,200,201,284,296,297], 2,4-dihydroxy-*s*-triazines[200,201,297], pyrimidines[133,139,279,298-305], steroid-annelated pyrimidines[310,311], purines[297,303,306], pyridines[307-309], pyrimido[4,5-*d*]pyrimidines and pyrazolo[3,4-*d*]pyrimidines[201,307-309]. The thermolysis of 6e gives *s*-triazine[131,133,295,296]. Some of these reactions are presented in Scheme 2.



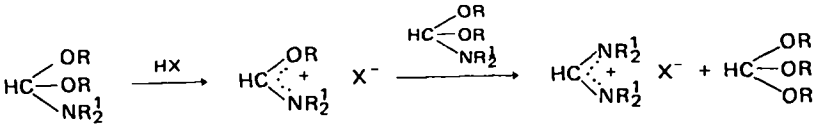
SCHEME 2

See also Section VII.

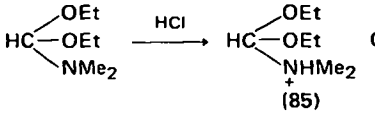
B. Reactions with Electrophilic Reagents

1. Inorganic acids, Lewis acids, carboxonium ions and carbonium ions

Strong anhydrous acids react with excess amide acetal to give formamidinium salts (equation 155)[180]. The ammonium salt **85** can be isolated by using HCl at low



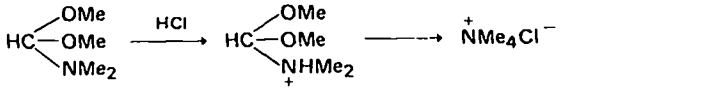
(155)



(156)

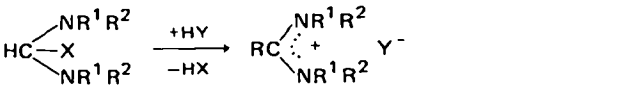
(85)

temperatures[11]. With excess amide acetal the end-product is a formamidinium chloride[180]. However, with HCl dimethylformamideacetal gives tetramethylammonium chloride (equation 157)[180,312]. Aminal esters[129] and triamino-



(157)

methanes[88,124,145,313] react with inorganic acids like HI, HCl, HBr, HBF_4 and H_2SO_4 to give formamidinium salts (equation 158).

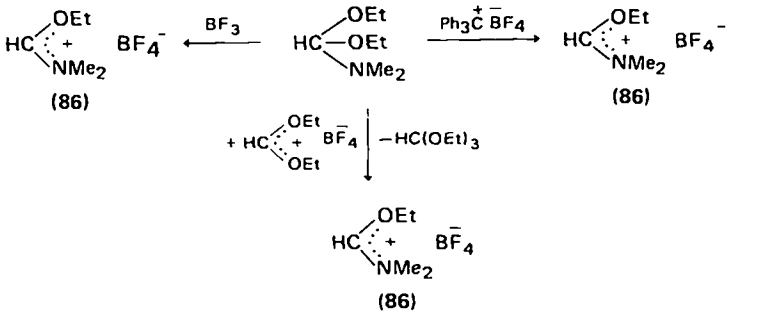


(158)

X = OR, NR^1R^2

Amide acetals transfer alkoxide ions to Lewis acids[10,11] carboxonium ions[11,314] and carbonium ions[11,314] with formation of the iminium salt **86** (equation 159). Similar reactions are possible with lactam acetals[11,314].

See also Section VII.



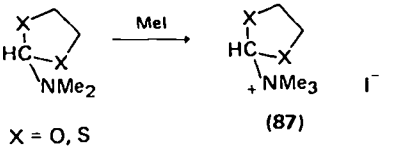
(159)

(86) **(86)** **(86)**

2. Alkylation

Alkylating agents which react by the S_N2 mechanism attack amide acetals firstly on the nitrogen[11,76,315-317]. In the case of cyclic *O,O*-acetals[11,76,317] or

S,S-acetals[316] the resulting salts **87** can be isolated. Non-cyclic amide acetals, e.g. dimethylformamide diethyl acetal, also undergo *N*-alkylation with methyl iodide. The complex reaction leads to a variety of products such as orthoesters, DMF, tetramethylammonium iodide and ethyl iodide[11]. *N*-alkylated orthoamides like **87** are also accessible from carboxonium ions and tertiary amines. They have been shown to be excellent dialkoxymethylation reagents able to form C–C, C–N and C–P bonds[91,104-107,317] (cf. Section II.A.5).

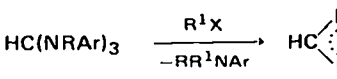


(160)

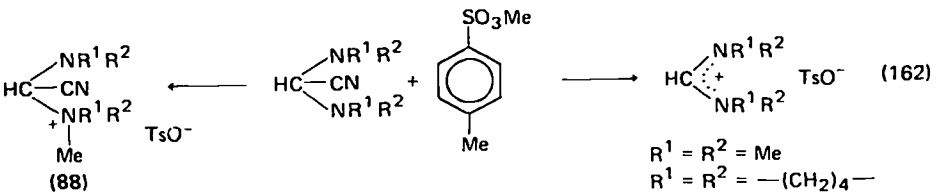
X = O, S

(87)

Tris(*N*-alkyl-*N*-arylamino)methanes react with alkylating agents to give formamidinium salts (equation 161)[88,124]. The strongly dissociated bis(dialkylamino) acetonitriles react similarly whereas weakly dissociated ones lead to *N*-alkylation products **88** (equation 162)[172]. Tosyl esters also react with dimethylaminomethoxyacetonitrile to give the stable salt **89** (equation 163)[318].



(161)



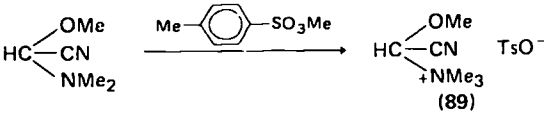
(162)

(88)

$R^1 = R^2 = Me$

$R^1 = R^2 = -(CH_2)_4-$

$R^1-R^2 = -(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$

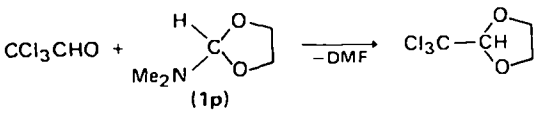


(163)

(89)

3. *Aldehydes and ketones, azomethines and azines*

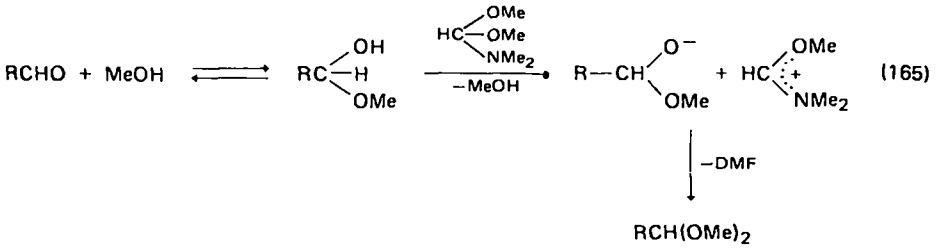
Because of their basic characteristics amide acetals react with aliphatic aldehydes (e.g. acetaldyde) non-uniformly (due, for example, to aldol formation)[319]. However, in the reaction of chloral with the cyclic amide acetal **1p**, the corresponding dioxolan can be isolated in 16% yield (equation 164).



(164)

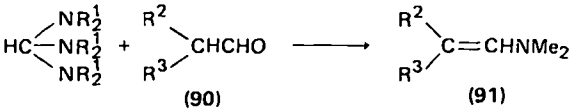
(1p)

The acetalation of aliphatic aldehydes succeeds in the presence of alcohols[319] similarly to the acetalation of aldehyde half-acetals with alkoxymethylene iminium



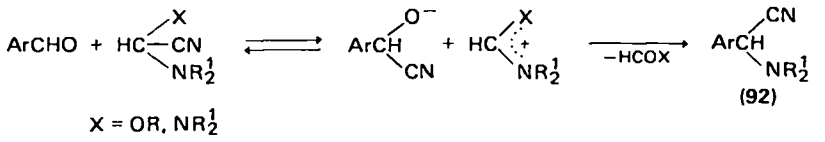
(165)

salts (equation 165)[193]. Tris(dialkylamino)methanes react with aldehydes **90** to give enamines **91** (equation 166)[320].



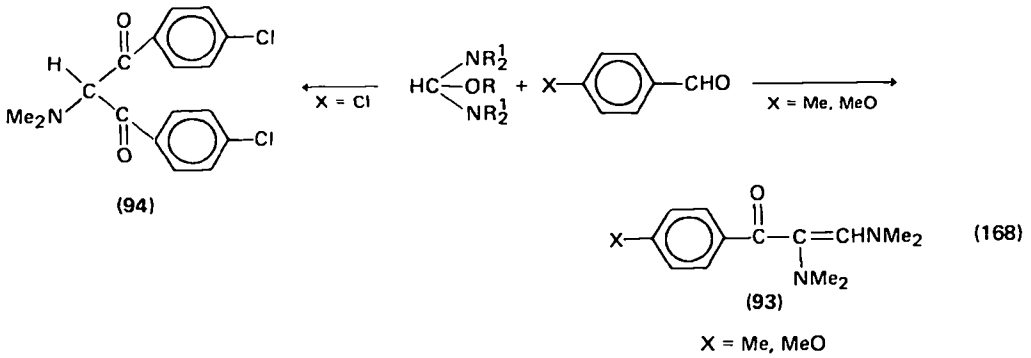
(166)

Cyclic amide acetals have some significance in the ketalation of steroidal ketones[195,321]. Aromatic aldehydes react with 1-dimethylamino-1-alkoxy or bis(dialkylamino) acetonitriles in a straightforward manner with formation of 1-dialkylamino-1-aryl nitriles **92** (equation 167)[149,172,322].

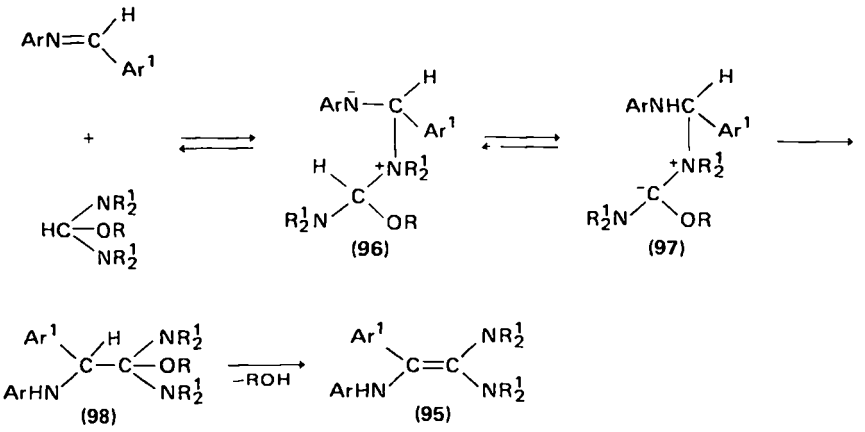


(167)

Aminal esters often react with aromatic aldehydes non-uniformly with frequent formation of hardly separable mixtures. From anisyl- or p-tolylaldehyde, ethylenes **93** are formed in moderate yields[125,323], whereas with *p*-chlorobenzaldehyde the diacylaminomethane **94** was isolated (equation 168).

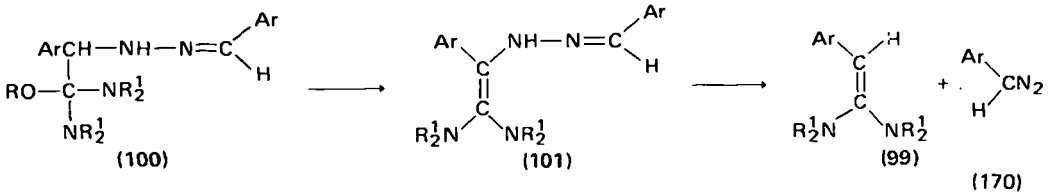


(168)



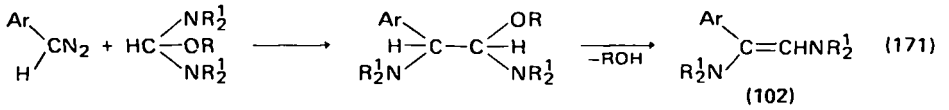
(169)

hinder the reaction. Under similar conditions azines yield ketene aminals **99** with 1,2-bis(dialkylamino)ethylenes (equation 170)[324]. The reaction can be explained



(170)

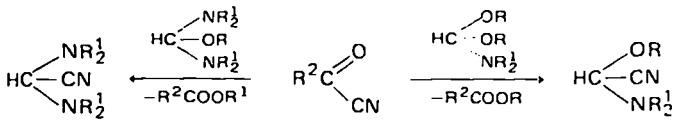
by formation of an *N*-adduct which rearranges to the intermediate **100**, analogously to **98**. By cleavage of aryldiazomethane from **101**, the ketanaminal **99** is formed. Depending on its stability, the aryldiazomethane can either decompose to give a diarylethylene or react with aminal ester to form a 1,2-diaminoethylene. The formation of the 1,2-diaminoethylene **102** from aminal esters and, for example, phenyldiazomethane can be proven (equation 171)[319].



(171)

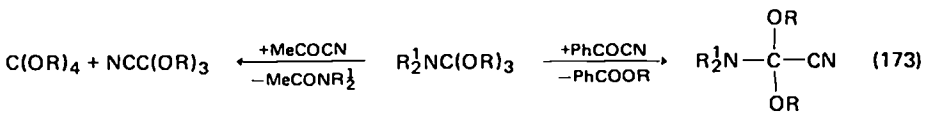
4. Acylating agents

Acyl cyanides react with amide acetals with primary formation of an *N*-adduct to give alkoxydialkylamino acetonitriles; analogously aminal esters give 1,1-bis(dialkylamino) acetonitriles[64] (equation 172). Orthocarbamic acid esters react with



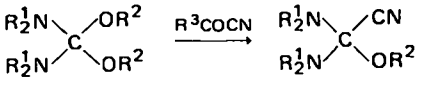
(172)

acetyl cyanide to yield a mixture of trialkoxyacetonitrile (**103**) and orthocarbonic acid ester (**104**). Dialkylacetamides are also formed, indicating a primary attack on nitrogen[190]. On the other hand, reaction with benzoyl cyanide gives a dialkyl-



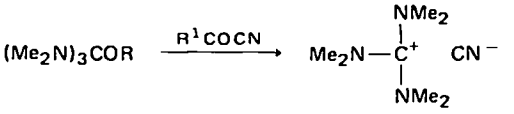
(104) (103) (105) (173)

aminodialkoxy acetonitrile (**105**) and benzoic acid esters[190] (equation 173). Both acetyl and benzoyl cyanide cleave urea acetals into dialkoxydialkylamino acetonitriles **106** (equation 174), whereas with tris(dimethylamino)alkoxymethanes



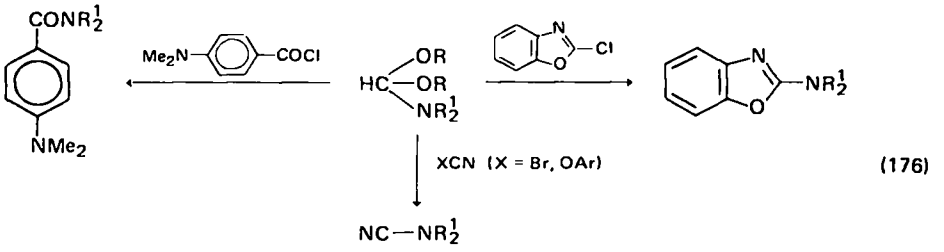
(106) (174)

hexamethylguanidinium cyanide **107** is formed (equation 175)[190]. These examples indicate that the nature of the reaction products with acylating agents depends upon the electrophilicity of the acylating agents as well as the nature of the substrate.



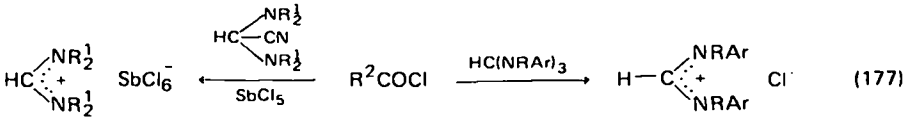
(107) (175)

p-Dimethylaminobenzoyl chloride[181], 2-chlorobenzoxazol[5], cyanogen bromide and cyanic acid esters[325] attack amide acetals on the dialkylamino group (equation 176). Tris(alkylarylamino)methanes[88] and bis(dialkylamino) acetonitriles[172] react



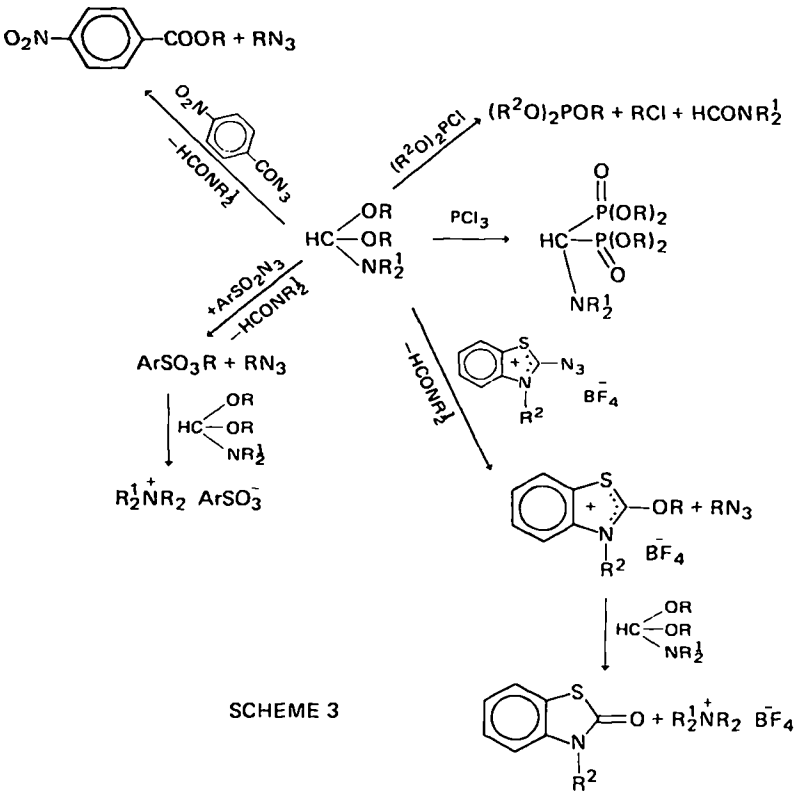
(176)

with acid chlorides or with acid chloride/$SbCl_5$ to give amidinium salts (equation 177).



(177)

The products which arise from a series of reactions of amide acetals with electrophiles indicate an attack on the oxygen of the alkoxy groups, as in the

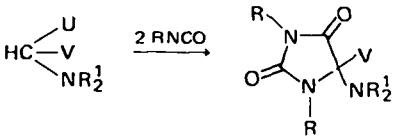


SCHEME 3

reactions with diketene (formed *in situ* from keten)[181], some acyl azides[326], sulphonyl azides[315], azidinium salts[315], phosphoric acid dialkyl ester chlorides[235] and PCl_3[327]. Only a few of these reactions (Scheme 3) take place in a simple manner, since the primary products can further alkylate or acylate the amide acetals in the reaction mixture (cf. Section IV.B.2).

5. *Heterocumulenes*

Isocyanates react with acyclic amide acetals[147,328], amide thioacetals[39,43,329] and tris(dialkylamino)methanes[214] to yield 5-substituted-5-dialkylamino-2,4-dioxo-imidazolines (**108**) (equation 178). 5-Alkoxy-5-dialkylamino-2,4-diarylimino or -2,4-



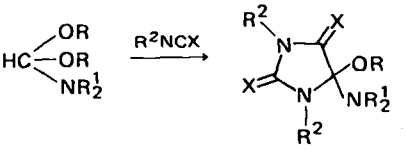
(178)

(**108**)

dithio imidazolines (**109**) were analogously obtained from diarylcarbodiimides[330] or isothiocyanates with small alkyl groups[146,331] and amide acetals (equation

179). On the other hand, isothiocyanates with bulky substituents provide *N,N,N'*-trisubstituted oxalic acid amide imide thioesters (equation 180)[146,331].

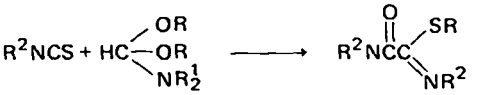
Dimethylformamide diethylacetal reacts with CS_2 to give a mixture of dithiocarbonic acid *-O,S* esters and *N,N*-dimethyldithiocarbamic acid esters[329]. Similar



(179)

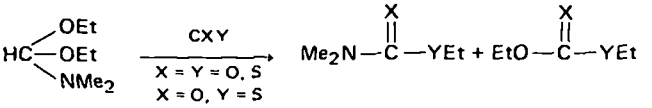
(109)

X = ArN, S



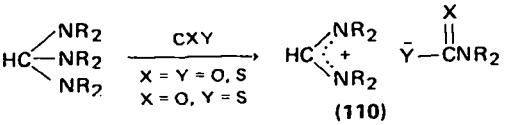
(180)

reaction mixtures were also obtained with CO_2 or COS[329] (equation 181). On the other hand, the reaction of aminal esters[329] or triaminomethanes[81,215] proceeds



(181)

uniformly with carbonic acid derivatives CXY to give formamidinium carbaminates **110** (equation 182).

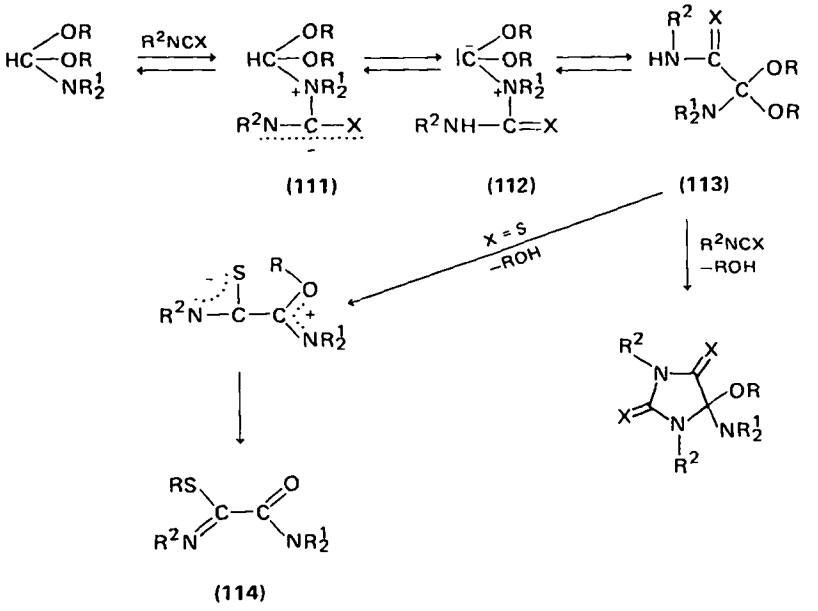


(182)

(110)

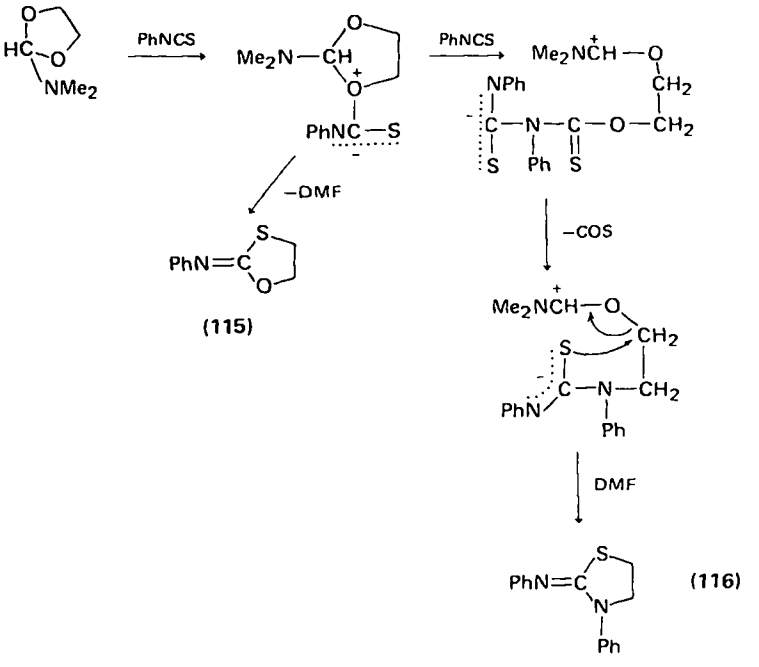
The mechanisms of the reactions of heterocumulenes with orthoamides have been thoroughly investigated[147,172,181,326]. The reactions start by formation of adducts on the orthoamide nitrogen, e.g. **111**. By the formation of adduct **111**, the formyl hydrogen of the orthoamides becomes acidic and may be transferred, by ylid formation **112**, to the heterocumulenes. Such an ylid can be trapped[147]. Furthermore, formamide acetals undergo H/D exchange of the formyl hydrogen (cf. Section IV.B.7). The ylid **112** undergoes a Stevens-like rearrangement, after which excess of the heterocumulene causes cyclization of the intermediate **113** which was obtained by the 1,2-shift. If the R^2 of the isothiocyanates is sterically demanding, then instead of a cyclization, alcohol is eliminated followed by an O → S transalkylation to give **114** (Scheme 4).

More complex is the reaction with cyclic amide acetals since in this case the heterocumulenes attack the ring oxygen[181,326], which leads to the formation of iminocarbonic acid derivatives **115** and **116** (Scheme 5).



(111) (112) (113) (114)

SCHEME 4

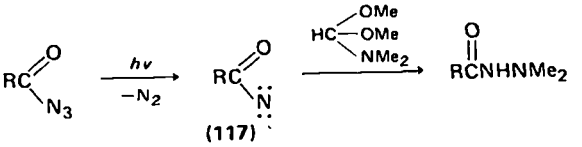


(115) (116)

SCHEME 5

Such reactions can also be performed with isocyanates which are produced *in situ* from acyl azides (equation 183)[326]. If the decomposition of the acyl azides is performed photochemically, then a nitrene intermediate **117** can be trapped[326].

See also Section VII.

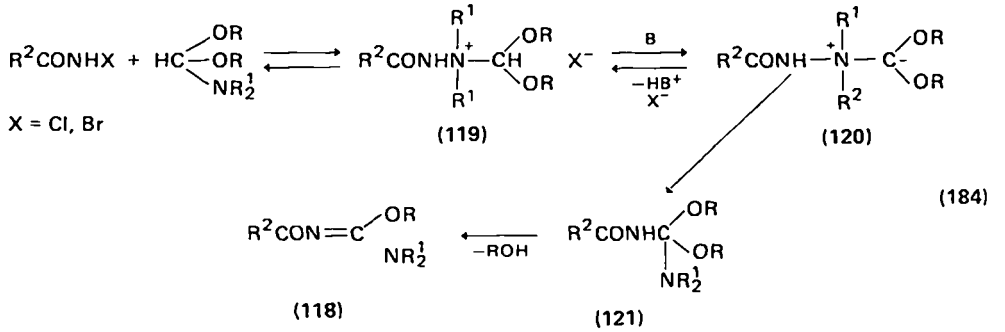


(183)

(117)

6. N-*Haloacyl amides*

N-Halogeno amides react with formamide acetals to yield acyl isocyanate *O,N*-acetals **118** (equation 184)[312,332,333]. The intermediary *N*-adducts **119** can be

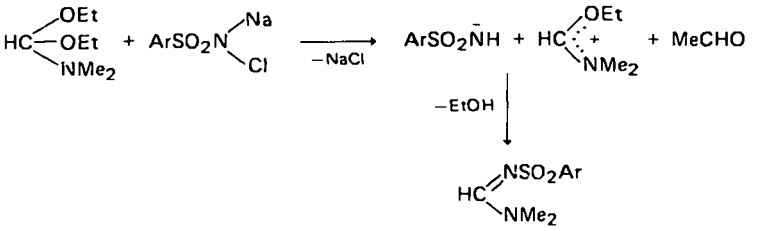


(184)

(119) (120) (118) (121)

isolated; they are deprotonated by bases (amide acetals or triethylamine) to form ylides (**120**). These ylides undergo a 1,2-shift to form *N*-acyl-*N'*,*N'*-dialkylurea acetals (**121**) which finally split off alcohols to give **118**. The hydrohalogenic acids which are formed during the reaction partially decompose tne amide acetals, whereupon orthoesters, formamidinium salts, ammonium salts, alcohols and amides are formed as by-products (cf. Section IV.B.1).

Aminal esters yield with *N*-halogeno amides predominantly formamidinium salts, besides small amounts of acylguanidines[333]. Triaminomethanes yield only formamidinium salts[333]. *N*-Halogeno sulphonamide sodium salts firstly oxidize amide acetals which leads finally to the formation of *N*-sulphonylformamidines (equation 185)[315].

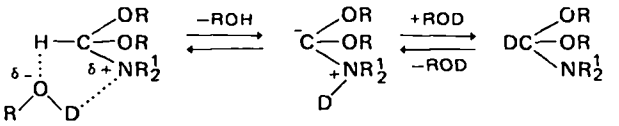


(185)

7. *H/D exchange of* N,N-*dialkylformamide acetals*

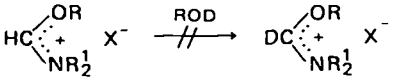
In the reaction discussed in Sections IV.B.3, IV.B.5 and IV.B.6, it was assumed that the adduct formation at the amide acetal nitrogen leads to acidification of the

formyl hydrogens. The same effect can result from protonation by hydrogen-bond formation. In agreement with this concept *N,N*-dialkylformamide acetals in the presence of deuterated alcohols (ROD), show H/D exchange of the formyl hydrogen (equation 186)[334-336]. The exchange is faster when the alcohol is more acidic



(186)

or the amide acetal is more basic[335] and is inhibited by bases[335,336]. A mechanism involving an alkoxy(dialkylamino)carbene[336] can be excluded since the iminium salt intermediates (122) postulated by this mechanism do not show any H/D exchange (equation 187)[335].

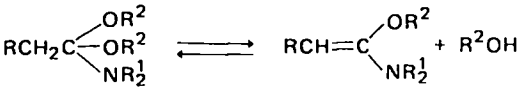


(187)

(122)

C. Reactions on the α-Methylene Groups of Amide and Lactam Acetals

Amide acetals containing CH_2 groups at the α-position of the orthoamide function are in equilibrium with ketene *O,N*-acetals (equation 188)[11,57], which

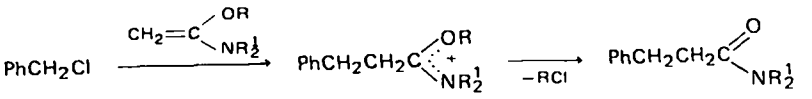


(188)

undergo facile reactions with electrophilic reagents. Strictly speaking, these are not typical orthoamide reactions, but reactions of electron-rich olefins. The above-mentioned equilibrium (188) is often used for various purposes and therefore these reactions will be shortly summarized in the following sections.

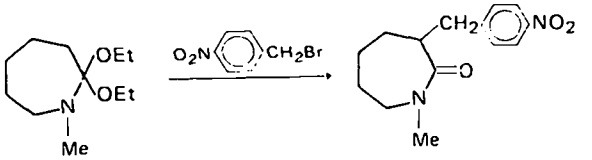
1. Alkylation and acylation

Benzyl halogenides react with the ketene *O,N*-acetals present in the equilibrium mixtures to yield iminium salts, e.g. **123**, which in turn decompose into alkyl halides and amides (equations 189 and 190)[337-339].



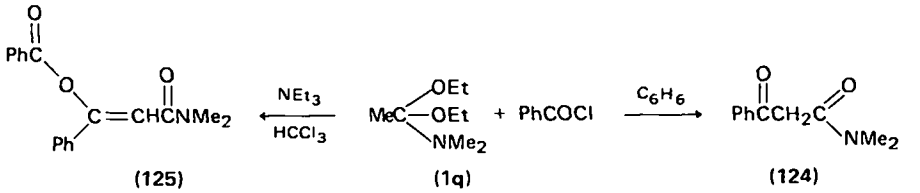
(189)

(123)



(190)

In principle, acylations take place by the same route[340]. In benzene the amide **124** is formed from **1q**. In chloroform in the presence of triethylamine the enol form of the primarily formed β-keto amides is also acylated to give **125** (equation 191). The acylation of lactam acetals gives similar results[271,339].

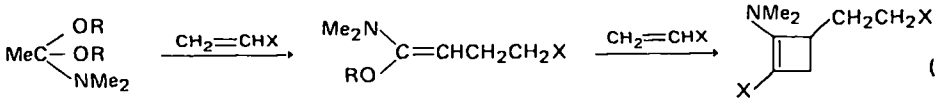


(191)

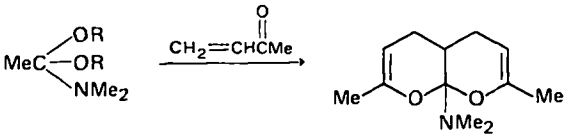
(125) (1q) (124)

2. *Reactions with activated alkenes and alkynes*

Electron-poor olefins like acrylonitrile or acrylates react with dimethylacetamide acetal by Michael addition. The resulting ketene *O,N*-acetals undergo cyclization by excess olefin (equation 192)[337]. The reaction with methyl vinyl ketone proceeds in a more complex manner to give the bicyclic amide acetal **1r** (equation 193)[337].

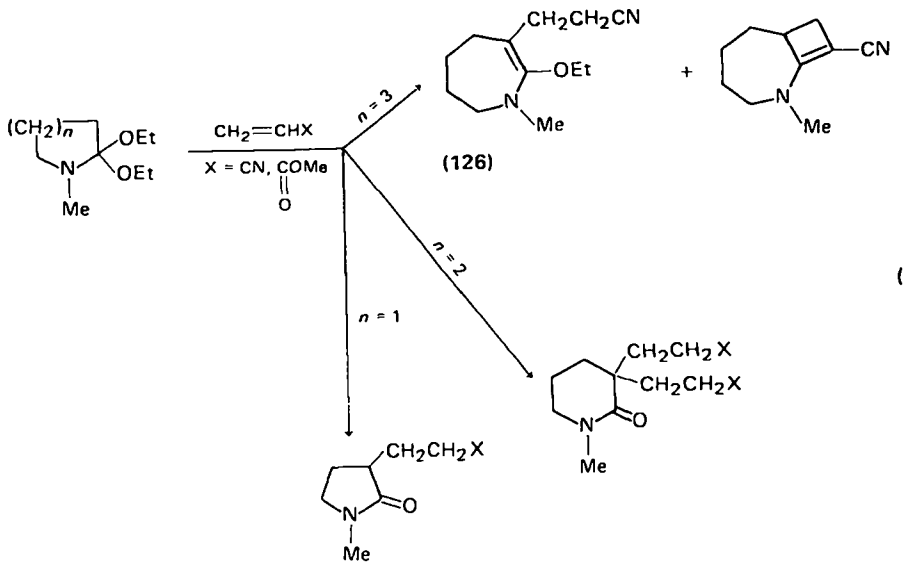


(192)



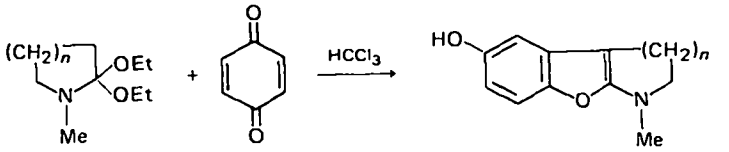
(193)

(1r)



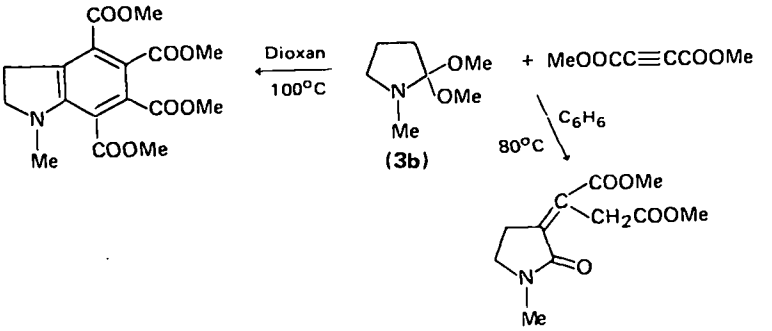
(194)

The nature of the products of the reaction of lactam acetals with electron-poor olefins depends on the ring-size. Possibly the ring-size influences the position as well as the rate of establishment of the equilibrium to form the ketene *O,N*-acetal. Only in the case of seven-membered ring lactam acetals[271] can an α-substitution product with a ketene acetal structure **126** be isolated together with the other products, while in the corresponding six-membered or five-membered lactam acetals, α,α-disubstituted or α-monosubstituted lactam acetals are formed (equation 194)[338,341]. Quinones react with lactam acetals to give annellated benzofurans (equation (195)[342]. From the lactam acetal **3b** and dimethyl acetylenedicarboxyl-



(195)

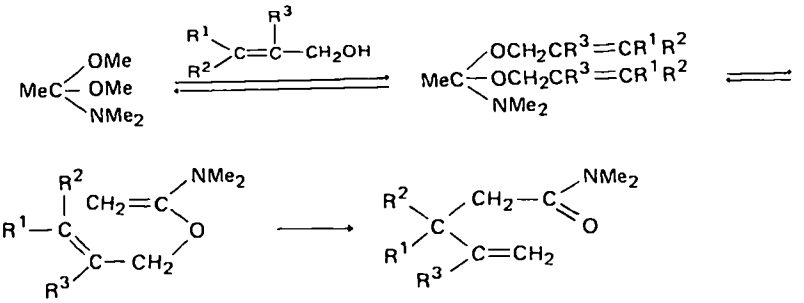
ate 1 : 1 or 1 : 2 adducts are formed depending on the reaction conditions (equation 196)[341].



(196)

3. *Allylic rearrangement*

Homologues of dimethylformamide acetals can be transacetalated with alcohols, including allyl alcohols. The amide acetals thus produced are in equilibrium with ketene *O,N*-acetals, and the latter undergo Claisen rearrangement by heating (equation 197). As starting materials, the following were used: dimethylacetamide



(197)

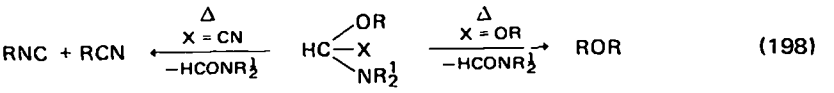
acetals[11,27,343-352], dimethylpropionamide acetals[353,354], dimethylbutyramide acetal[27] and lactam acetals[40,352]. As the alcoholic component, the following were found to be suitable: Allyl alcohol[11], cyclohexenols[343], 1,3-dienols[353,354],

benzyl alcohols[343], alkinyl-allyl alcohols[351], propargyl alcohols[349], allene alcohols[40,352], 3-(hydroxymethyl)pyridine[27] and 1-methyl-3-(hydroxymethyl)-pyridone-(2)[27].

See also Section VII.

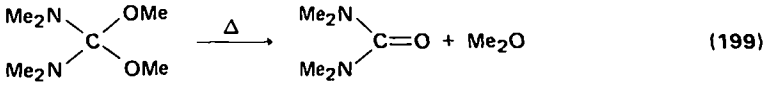
4. Pyrolysis and elimination reactions of orthoamides

High-boiling amide acetals decompose at elevated temperatures into amide and ether[26]. Alkoxy(dialkylamino) acetonitriles yield on thermolysis a mixture of alkyl nitrile and isonitrile[355] (equation 198). Even at lower temperatures (80–140°C) a

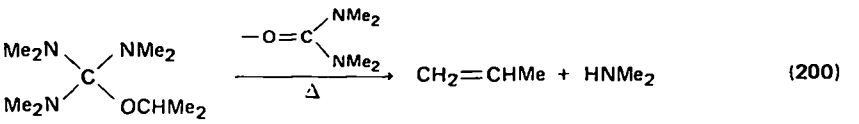


(198)

similar decomposition is observed with urea acetals (equation 199)[159] or tris(dimethylamino)isopropyloxymethane (equation 200)[165]. A remarkably easy decom-

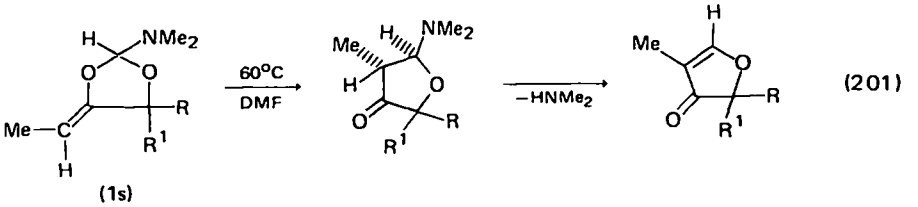


(199)



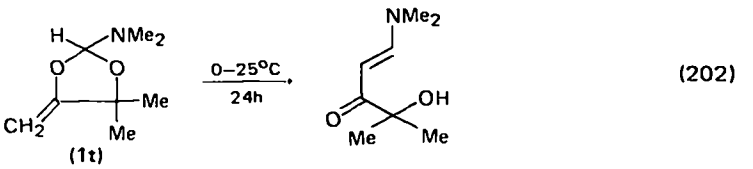
(200)

position is observed with cyclic amide acetals **1s** and **1t** (equations 201 and 202)[356].



(201)

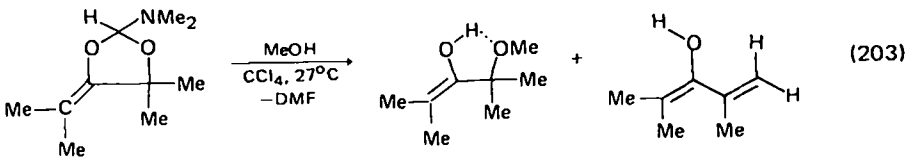
(1s)



(202)

(1t)

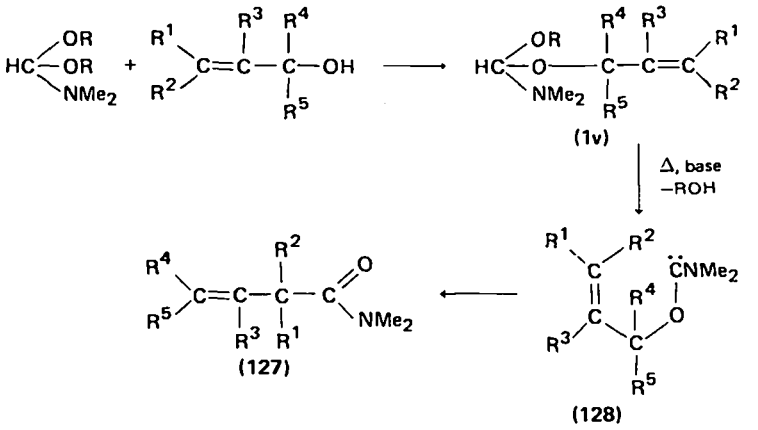
2-Dialkylamino-4-alkylidene-1,3-dioxolanes, e.g. **1u**, are cleaved under acid catalysis even at room temperature to give DMF and stable enols (equation 203)[356–359].



(203)

(1u)

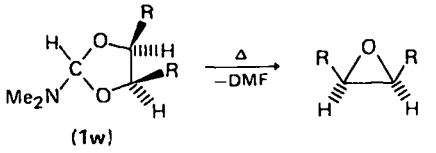
A remarkable rearrangement was discovered in the reaction of DMF-acetals with allyl alcohols (equation 204)[360]. Amide acetals **1v** are reformed through deacetala-



(204)

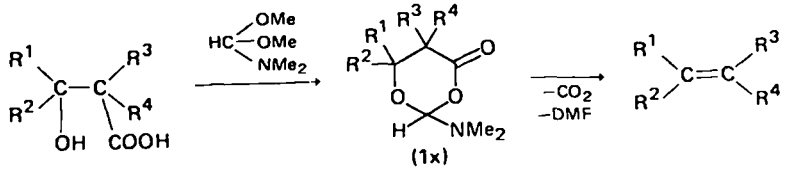
tion, yielding by thermolysis the homologous amide **127**. A carbene (**128**) was proposed as the intermediate product, which rearranges by a 2,3-sigmatropic rearrangement into the amide **127**.

Prolonged heating of cyclic amide acetals **1w** leads, under expulsion of DMF, to epoxides (equation (205)[361]. β-Hydroxy acids yield olefins upon heating with



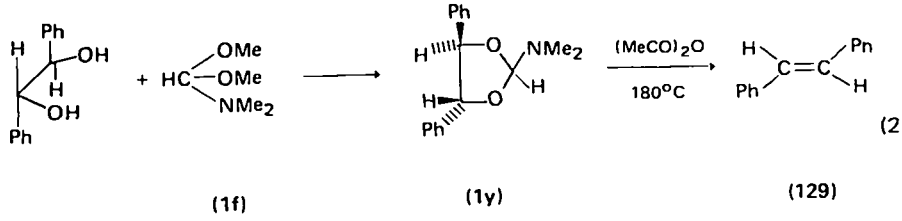
(205)

amide acetals. A cyclic amide acetal **1x** was proposed as intermediate (equation 206)[362]. 1,2-Diols react with the acetal **1f** to give the cyclic amide acetal **1y**, which



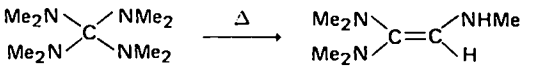
(206)

in turn yields the olefin **129** upon heating with acetic anhydride (equation 207)[363]. Pyrolysis of tetrakis(dimethylamino)methane proceeds via radicals to



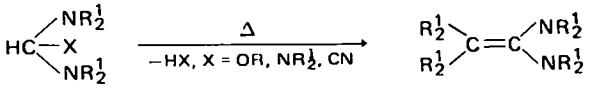
(207)

yield 1,1-bis(dimethylamino)2-methylaminoethylene (equation 208)[364]. The thermolysis of aminal esters, triaminomethane and bis(dialkylamino) acetonitriles

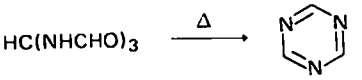


(208)

which leads to tetraaminoethylenes probably takes place through a bis(dialkylamino)carbene (equation 209)[58,81,84,114,136,137,152,365-368]. Tris(formylamino)methane provides *s*-triazin on heating (equation 210)[131,133,295,296].

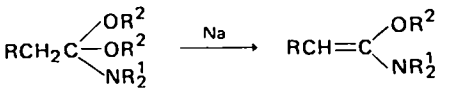


(209)



(210)

The equilibrium between ketene *O,N*-acetals and homologues of formamide acetals has already been mentioned. Pure ketene *O,N*-acetals are obtained by heating of the equilibrium mixture with sodium (equation 211)[11], calcium[57] or sodium hydride[60] (cf. Section II.A.1.)



(211)

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VII. ADDENDUM

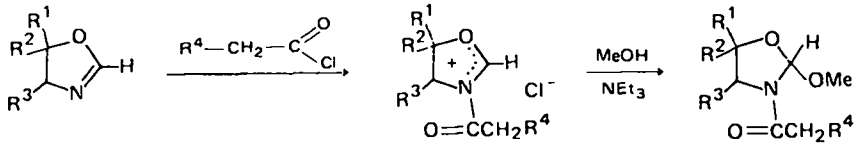
To Section I, p. 534.

Recently an additional brief review dealing with the chemistry of amide acetals and lactam acetals has been published[369].

To Section II.A.1, p. 537.

Further lactam acetals have been prepared by alkylation of lactams, using oxonium salts as alkylating reagents, and further reactions of the iminium salts thus formed with alkali alcoholates[370,371].

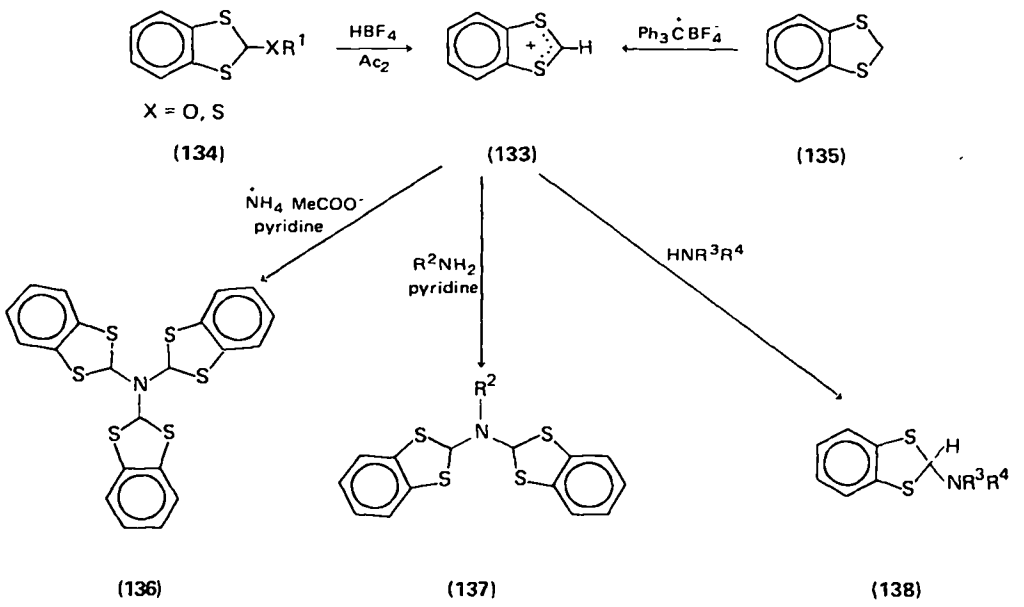
By acylation of oxazolines (**130**) iminium salts (**131**) can be prepared which are useful starting materials for amide acetals (**132**)[372].



(130) (131) (132)

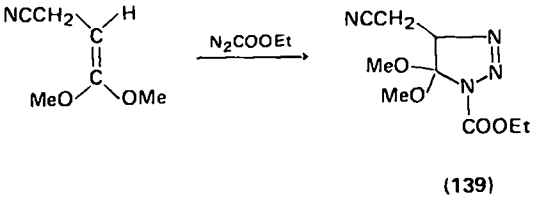
To Section II.A.5, p. 541.

The salt **133** which is obtainable from orthoesters (**134**) or the dithioformal (**135**), on treatment with ammonia[373], primary amines[373] or secondary amines[373,374] respectively yields amide thioacetals **136**, **137** and **138**.



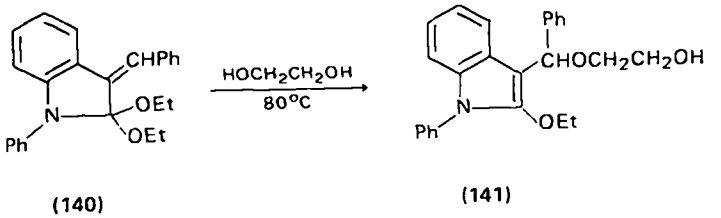
To Section II.A.8, p. 545.

From ketene acetals and ethyl azidoformate further heterocyclic amide acetals, e.g. **139** have been prepared[375].

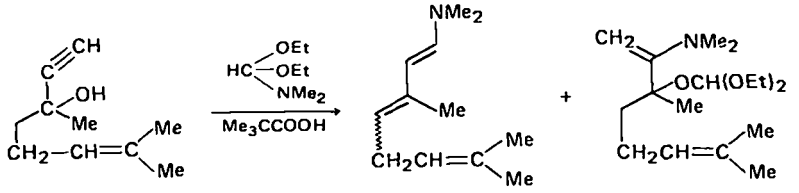


To Section IV.A.2, p. 557.

Action of glycol on the lactam acetal (**140**) doesn't produce a spirocyclic 1,3-dioxolane via transacetalation instead the indole derivative (**141**) is formed[370].



Alcoholysis of dimethylformamide acetals by alkynols (**142**), e.g. in the presence of pivalic acid, affords a mixture of dienes (**143**) and orthoesters (**144**)[376].



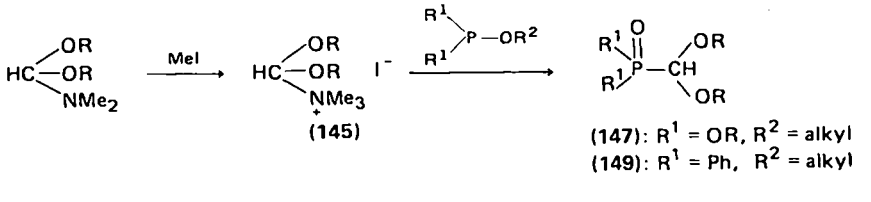
(142) (143) (144)

To Section IV.A.4.a, p. 562.

Further NH_2-acidic compounds such as primary amines[377], hydrazino pyridmidines[378], β-amino-acrylic acid esters[379,380], acrylic acid amides[381], aminouracils[382], ureas[371], guanidines[371], amidines[371] and thiourea[371], have been reacted with amide acetals[377-379,382] and lactam acetals[371,379-381] to form amidines.

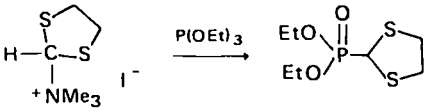
To Section IV.A.5, p. 564.

N-quaternized amide acetals (**145**)[383] or thioacetals (**146**)[384], which were prepared *in situ*, have been reacted with phosphoric acid esters and phosphinic acid esters to give acetals of formyl phosphonic acids (**147**, **148**) or diphenyl formylphosphine oxide (**149**), respectively.



(145)

(147): R^1 = OR, R^2 = alkyl
(149): R^1 = Ph, R^2 = alkyl



(146) (148)

To Section IV.A.7.a, p. 566.

A number of enamines was synthesized by action of dimethylformamide acetals[385,386] or aminal esters[387-389] respectively on CH_2-acidic compounds such as nitrotoluenes[385], α-oxo-lactones[386], ketones[387,388] and naldixinic acid derivatives[389].

To Section IV.A.8.a, p. 569.

Further difunctional compounds have been cyclized with the aid of dimethylformamide acetals to form bis-chromones[390], 2-triazolo[1,5-*b*]isoquinolin-5(1*H*)-ones[391] and 1,2-dihydro-6*H*-*s*-tetrazino[2,3-*b*]isoquinolin-6-ones[391].

To Section IV.A.8.b, p. 570.

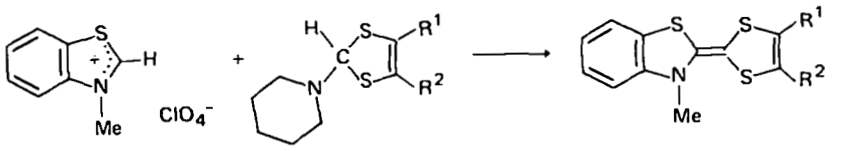
Numerous condensation products, formed by action of orthoamides on CH_2- or NH_2-acidic compounds, have been used for the synthesis of heterocyclic compounds. From these starting materials were prepared indoles[385], pyrazoles[389], isoxazoles[389], pyrimidines[389], annellated pyrimidindiones[382,387], heterocyclic annellated pyrimidines[386], 2-pyridones[381], theophyllin[382], pyrimido[4,5-*b*]-indoles[371], *s*-triazolo[1,5-*c*]pyrimidine[378] and 4-pyridones[379].

To Section IV.A.8.c, p. 571.

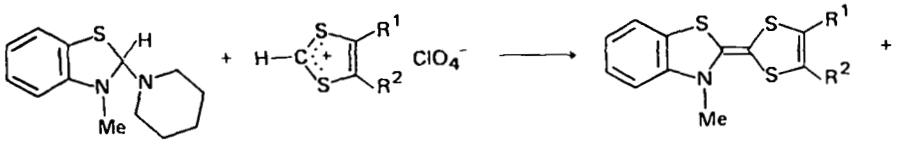
The reaction between tris(formylamino)methane on the one hand and α- and β-tetralone[392] as well as 1,3-dihydroxynaphthalene[393] on the other affords annellated pyrimidine derivatives.

To Section IV.B.1, p. 572.

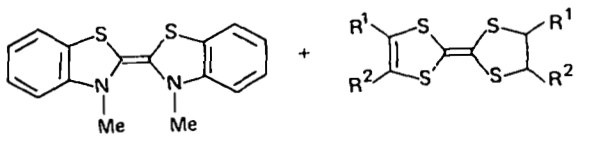
Amide thioacetals (**150**) react with benzthiazolium salts (**151**) to form the electron-rich olefins **152**[394]; analogously, the action of dithioliumsalts **153** on the aminal thioester **154** produces a mixture of olefins (**152, 155, 156**). For this reactions nucleophilic carbenes were proposed as reactive intermediates[394].



(151) (150) (152)



(154) (153) (152)



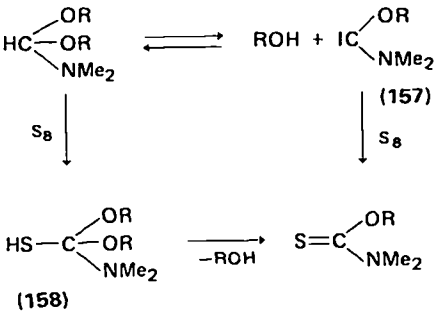
(155) (156)

To Section IV.B.5, p. 578.

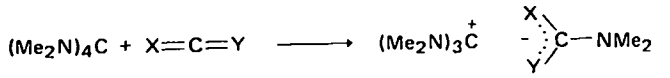
The reaction of amide acetals with isocyanates and isothiocyanates has been reinvestigated[395]. In the course of this work a reaction mechanism involving dimethylaminoalkoxycarbenes as intermediates was assumed[395]. This reaction mechanism already had been taken into consideration by Bredereck and coworkers some time ago[146,147,181]. The more recent results, however, based on concur-

rence experiments, may be explained both by a nucleophile carbene and by an adduct mechanism.

The reaction of elemental sulphur with amide acetals giving thiourethanes[395], can be explained via a dimethylaminoalkoxycarbene (157) or also via CH-insertion into the amide acetal molecule followed by loss of alcohol from the orthocarbonic derivative 158 thus formed. Therefore further investigations will be necessary to decide if the reactions of orthoamides with electrophilic reagents proceed via a carbene mechanism or via an adduct mechanism exclusively. Possibly both mechanisms contribute simultaneously to product formation with different amounts (according to different reaction velocities for each mechanism), depending on reaction conditions. Tetrakis(dimethylamino)methane reacts with CO_2, COS and CS_2 to form guanidinium salts (159)[396].



(158)



(159)

To Section IV.C.3, p. 583.

Further examples of Claisen rearrangement using dimethylacetamide acetals and alkynoles[397] and 3-arylallyl alcohols[398] as starting materials have been published.

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Supplement B The Chemistry of Acid Derivatives
Edited by Saul Patai

CHAPTER 10

Detection and determination of acid derivatives*

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*No reference appears in this chapter to the detection and determination of acids and acyl halides as no significant developments have taken place since the appearance of the relevant main volumes of the series.

I. AMIDES AND LACTAMS

A. Introduction and Miscellaneous

Amides of the type $RCONH_2$ are neutral, or at most, very weakly basic materials owing to the combination of an acid-forming and a base-forming group. The major importance of amides lies in their relationship to the structure of peptides, proteins and pharmaceutical materials[1].

There are several methods available which may be employed to estimate amides. Macroprocedures have been reviewed by Hillenbrand and Pentz[2] and micro and semimicro methods by Cheronis and Ma[3].

Amides are difficult to hydrolyse but the hydrolysis proceeds slowly and smoothly albeit under rather drastic conditions since they are much less reactive than esters; one equivalent of alkali is consumed on saponification (equation 1).

$$R^1CONR^2_2 + KOH \longrightarrow R^1COOK + R^2_2NH \quad (1)$$

Primary amides are hydrolysed by heating with concentrated sodium hydroxide solution to liberate ammonia. Hot aqueous mineral acids act similarly. Lithium aluminium hydride quantitatively reduces amides to the corresponding amines (equation 2). Primary and secondary amides react with methylmagnesium iodide to

$$2\,RCONH_2 + LiAlH_4 \longrightarrow 2\,RCH_2NH_2 + LiAlO_2 \quad (2)$$

liberate methane. Dehydration of a primary amide may be achieved by reaction with 3,5-dinitrobenzoyl chloride, the product being a nitrile. Amides containing the grouping $RCONH_2$ react with nitrous acid to evolve nitrogen and form the corresponding acid (equation 3). This behaviour is general and its value lies in the fact

$$RCONH_2 + HNO_2 \longrightarrow RCOOH + H_2O + N_2 \quad (3)$$

that it provides an alternative to hydrolysis for the conversion of amides into acids.

The Hofmann rearrangement of primary amides has been applied to quantitative analysis. Reaction of amides with hypochlorous or hypobromous acid yields chloro- or bromo-amides, halogen replacing a hydrogen of the amino group. Subsequent hydrolysis with excess aqueous alkali yields the corresponding amine (equation 4). Unfortunately the reaction is seldom quantitative. An interesting

$$RCONH_2 \xrightarrow{KOBr} RCONHBr \xrightarrow{KOH} RCNO \longrightarrow RNH_2 + CO_2 \quad (4)$$

feature of this reaction is that if the amide used exhibits optical activity it is retained in the amine product.

Amides may be determined qualitatively and quantitatively by their reaction with hydroxylamine sulphate and iron III chloride[4]. The amide reacts with hydroxylamine to form the corresponding hydroxamate which, on treatment with iron III chloride, develops a brown-violet colour (equation 5). The stability of the colour

$$RCONH_2 + NH_2OH \longrightarrow NH_3 + RCONHOH \xrightarrow{Fe^{3+}} \text{ferric hydroxamate} \qquad (5)$$

depends mainly on the ferric and hydrogen ion concentrations of the final solution[5]. The amide reaction occurs more slowly than that which occurs with esters, anhydrides, acid chlorides and imides so that amides may be deemed as constituting an interference in the detection and estimation of the more rapidly reacting species[6]. However, in many cases esters and amides may be determined successively by the same method, for example ethyl acetate and acetamide[4]. The method is not very successfully applied to the determination of diacyl amides[7]. The factors affecting the stability[8] of the hydroxamic acid–iron complex and the kinetics and mechanisms[9] have been studied in detail.

A comprehensive review of the methods available for the detection and estimation of amides has been reported[10]. Knecht[11] has described in detail the purification of *N*-methylacetamide and some of the tests applied as a criterion of purity. Water was determined using Karl Fischer reagent, and the specific conductance, polarographic range, melting point, colour and odour were also reported. The reduction potentials of a series of amides have also been recorded[12]. Amides may be detected by spot tests, the methods for which have been recorded by Feigl and Anger[13]. The substituted monoamide of phthalic acid has been determined photometrically[14].

A method which, it is claimed, is sensitive and accurate for the rapid analysis of aqueous solutions of a variety of amides has been reported[15]. The amide functional group is subjected to oxidation by bromine, and the excess bromine is destroyed with sodium formate. The amide oxidation product oxidizes iodide ion to iodine which is measured as the triiodide–starch complex. The procedure is specifically designed for primary amides but may be modified to permit the determination of secondary amides. Primary and secondary amines interfere. Acetonitrile also apparently interfered, but the interference was traced to the presence of acetamide, the primary hydrolysis product of acetonitrile. Consequently the method may be adapted to determine trace concentrations of amides in acetonitrile.

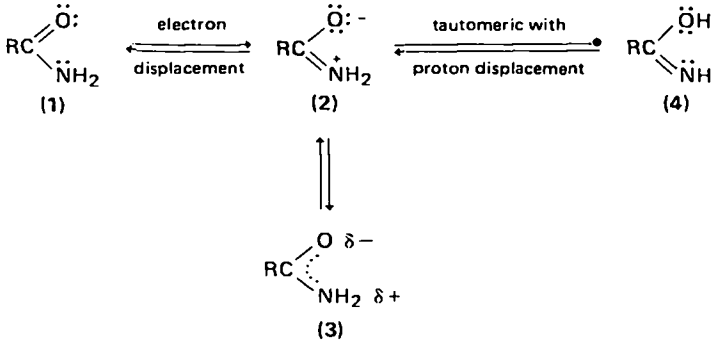
A method, not specifically applicable to amides, has been described for the determination of active hydrogen by chemical ionization mass spectrometry[16]. At a pressure of 0.4 torr electron bombardment of deuterium oxide (D_2O) affords abundant ions, which in turn function as Brönsted acids in the gas phase and deuterate many organic compounds. Additionally, because of the relatively high source pressure, sufficient collisions occur between the sample and deuterium oxide to exchange all the active hydrogen atoms attached to nitrogen, oxygen and sulphur atoms for deuterium in the organic molecules.

Lactams are cyclic amides of amino acids. Their primary importance lies in their relationship to the structure of many pharmaceutical preparations, for example the penicillins[1] and cephamycins[17]. Methods for the detection and estimation of amides may be applied to the lactam function[18,19]. Lactams are hydrolysed by strong acids to yield the corresponding amino acid and since the latter is generally a weak acid it may be determined in the presence of mineral acid by differential

titration. The colorimetric estimation of lactams parallels that applied to amides in that the lactam is reacted with hydroxylamine to form the hydroxamic acid which is then treated with iron III ions to form a coloured complex. The optimum experimental conditions and wavelength at which maximum absorbance occurs varies with individual compounds.

B. Infrared and Raman Spectra

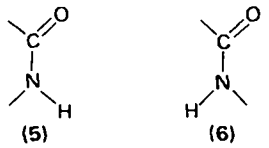
The amide functional group (1) exhibits considerable internal $p-\pi$ conjugation as indicated by the following structures:



The greater mobility of the unshared electrons in nitrogen compared to oxygen and the greater electronegativity of oxygen favour structures 2 and 3. Consequently the bond order of the carbon–oxygen bond decreases and that of the carbon–nitrogen bond increases. The net result is that the carbonyl group wavenumbers are lower and the carbon–nitrogen wavenumbers are higher than expected. In theory the amide group could exist in the tautomeric iminohydrin structure (4) but no real evidence has ever been presented for its existence.

All primary and secondary amides are expected to exhibit characteristic wavenumbers associated with the carbonyl, carbon–nitrogen and nitrogen–hydrogen bonds. Tertiary amides do not exhibit infrared and Raman wavenumbers associated with the nitrogen–hydrogen bond.

As a consequence of conjugation the amide group is planar and free rotation about the partially double carbon–nitrogen linkage is restricted leading to the possibility of *cis* (5) and *trans* (6) isomers.



Amide absorptions are principally associated with three groups of infrared and Raman wavenumbers: 3600–3050 cm^{-1}, 1700–1450 cm^{-1} and 1400–1300 cm^{-1}, of which the latter is of the least importance. A further complication is introduced by the complexity of the amide group and is evidenced as a partial breakdown of the group frequency/wavenumber concept. Bellamy[20,21] tabulates wavenumbers (cm^{-1}) for six amide bands identified as amide I to amide VI.

The amide I, II and III bands are primarily associated with the carbonyl stretching, nitrogen–hydrogen deformation and carbon–nitrogen stretching coupled with a nitrogen–hydrogen vibration, respectively. The amide IV band is observed in the region around 630 cm^{-1} and 780 cm^{-1} in the spectra of secondary (monosubstituted) amides of the type R^1CONHR^2 and HCONHR, respectively and arises principally from the O···C···N bending mode. The amide V vibration, principally nitrogen–hydrogen out-of-plane bending, and the amide VI vibration, principally carbonyl out-of-plane bending, generally appear as weak absorptions in both infrared and Raman and are usually of little use for characterization purposes.

The characteristic wavenumbers of *N*-deuterated secondary amides have been labelled as amide I′, amide II′ etc. by Miyazawa[22]. An alternative assignment for the amide II band has been proposed by Hallam[23] who suggests that in most primary and secondary amides the amide II mode is essentially $\delta(NH_2)$ or $\delta(NH)$ and the amide III $\nu(CN)$. To account for the behaviour of these molecular types upon deuteration it is suggested that $\delta(NH)$ shifts by approximately $\sqrt{2}$ to near 1200 cm^{-1} and that this $\delta(ND)$ interacts strongly with the $\nu(CN)$ which has also slightly shifted in going from OCNH to OCND, to give rise to the amide II′ and amide III′ bands respectively.

Because of its relevance to polypeptide chemistry the amide group has been extensively subjected to force-field calculations[24]. The amide I vibration is often referred to as the carbonyl stretching mode. However, by studying formamide and its deuterated analogues Suzuki[25] has demonstrated that the band arises from a mixed vibration involving 64% carbonyl stretch and 33% carbon–nitrogen stretch. In acetamide[26] the percentages are 59 and 28 for the carbonyl stretch and nitrogen–hydrogen bending respectively. The amide I band for secondary amides is attributed mainly to the carbonyl stretching mode (70–80%) but the carbon–nitrogen stretching and nitrogen–hydrogen bending modes contribute 10–30% and 10–20% respectively.

The amide II band in primary amides arises principally from the symmetric nitrogen–hydrogen bending or scissors vibration. Suzuki[26] attributes 85% nitrogen–hydrogen bending and 17% carbonyl stretching to this mode in acetamide. The amide II band in the *trans* form of *N*-methylformamide[27] has been shown to consist of 60% nitrogen–hydrogen bending and 32% carbon–nitrogen stretching. In *trans*-*N*-methylacetamide the values are ~60% and ~40% respectively[28].

In *cis* secondary amides there is no coupling of the carbon–nitrogen stretching and nitrogen–hydrogen bending modes[29]. However, in *cis*-*N*-methylacetamide the band at 1445 cm^{-1} is suggested as having 78% nitrogen–hydrogen bending character and the band at 1386 cm^{-1} as having 71% carbon–nitrogen stretching character[30]. Changes in these percentages are observed for the *N*-deuterated species. In the *trans* form the interaction raises the amide II band to wavenumbers greater than the methyl and methylene group deformation wavenumbers.

The amide III vibration is also attributed to the interaction between carbon–nitrogen stretching and nitrogen–hydrogen bending modes and is usually observed at lower wavenumbers than the pure carbon–nitrogen stretch as found in the *cis* configuration. In *trans*-*N*-methylformamide[27] this vibration is endowed with 33% and 36% character of the two modes whereas in *trans*-*N*-methylacetamide the values are 35% and 29% respectively[28].

The band wavenumbers for amides have been tabulated by Bellamy[31] and Katon and coworkers[32]. Raman-effect values are available from Kohlrausch[33] and Dollish and coworkers[34]. The spectroscopic evidence for conformational isomerism of the amide group has been reviewed by Hallam and Jones[35].

1. Primary amides

a. Nitrogen–hydrogen stretching vibrations. Dilute solutions of primary amides in non-polar solvents absorb near 3530 and 3415 cm^{-1}, corresponding to the antisymmetric and symmetric stretching modes of the NH_2 group, respectively. The intensity of these bands is generally higher than in the corresponding amines. In concentrated solutions and in the liquid and solid states hydrogen bonding shifts the absorptions to lower wavenumbers, the antisymmetric and symmetric stretching modes occurring near 3350 and 3180 cm^{-1}, respectively.

b. Amide I vibration (carbonyl stretching). All primary amides exhibit strong absorption between 1715 and 1650 cm^{-1}, the position and intensity of which depends on the physical state, nature of the solvent and concentration. In the associated state the vibration occurs near 1650 cm^{-1} whereas in the non-bonded state the wavenumber shifts to the range 1715–1675 cm^{-1}. The amide I band of acetamide is unusual in that it is resolved into two bands at 1714 and 1695 cm^{-1} in carbon tetrachloride solution. As the concentration is increased the intensity of the low wavenumber band increases whilst that of the higher decreases. The effect is probably due to the perturbation of the monomer $\rightleftharpoons$ trimer equilibrium[36]. The amide I band position is affected by substitution on the nitrogen atom and by ring strain; α-halogenation shifts the band to a slightly higher wavenumber. The integrated intensity of the band in non-bonded aromatic amides is higher than in non-bonded aliphatic amides but in the solid state the differences are hardly noticeable.

c. Amide II vibration. This band occurs in the range 1620–1580 cm^{-1} for the non-associated species and in the range 1650–1620 cm^{-1} for the associated species. The band is weaker and of more variable position being dependent on solvent, structure and physical state of the amide. In concentrated solutions four bands may be observed arising from the amide I and II vibrations of free and associated molecules present in equilibrium. It is worthy of note that the intensity of the amide II band is a factor of two or three times weaker than the amide I band and that the amide II band moves to lower wavenumber upon dilution.

d. Other vibrations. Primary alkyl amides consistently exhibit a band in the region 1420–1390 cm^{-1} in the infrared and Raman but it is of limited analytical value. It has been assigned to what has been conveniently described as a carbon–nitrogen stretching mode. The rocking mode of the NH_2 group occurs as a band of medium intensity in the range 1150–1100 cm^{-1} in the Raman effect[34]. Other bands are observed in the ranges 600–550 cm^{-1} and 500–450 cm^{-1} but their analytical value is debatable.

2. Secondary amides

a. Nitrogen–hydrogen stretching vibrations. In dilute solutions in non-polar solvents secondary amides exhibit a single absorption band in the 3500–3400 cm^{-1} region which is assigned to the unassociated nitrogen–hydrogen bond. However, the situation is not clear-cut as secondary amides may occur as *cis* and *trans* isomers. In non-associated secondary amides the absorption due to the *trans* isomer occurs in the range 3495–3420 cm^{-1} and that for the *cis* isomer in the range 3440–3400 cm^{-1}. In the associated state the band is located near 3300 cm^{-1}. A review by Hallam and Jones[35] provides very much greater detail. However, since the *trans* form is always predominant in *N*-alkyl amides the characteristic band wavenumbers in the infrared and Raman should be studied carefully as they are

usually those attributed to the *trans* form. Alternatively, sterically hindered amides, e.g. *N*-*t*-butylphenylacetamide, exist predominantly in the *cis* form.

b. Amide I vibration. The band wavenumber in amides of the type R^1CONHR^2 depends on the nature of the groups R^1 and R^2, the physical state, concentration and polarity of the solvent. Open-chain *trans* *N*-monosubstituted amides absorb in the range 1680–1630 cm^{-1} in the solid and liquid states and in the range 1700–1650 cm^{-1} as dilute solutions in non-polar solvents. The *cis* form also absorbs in these regions. Groups substituted onto the nitrogen atom produce inductive and conjugative effects which affect the band wavenumber[37]. The band of *N*-aryl amides normally occurs at higher wavenumber than in the corresponding *N*-alkyl amide, the affect usually being attributed to conjugation between the benzene ring and the nitrogen atom which weakens the conjugation within the CONH group, thereby increasing the carbon–oxygen bond order.

c. Amide II vibration. The band occurs between 1570 and 1480 cm^{-1}, the intensity being lower than that of the amide I band. For the associated *trans* form the absorption occurs in the range 1570–1510 cm^{-1} and between 1550–1480 cm^{-1} in the non-associated form. No band is observed in this region for the *cis* configuration. Strong influences are exerted on the band wavenumber by the physical state of the amide. Thus in *N*-methylacetamide the band is observed at 1565, 1534 and 1490 cm^{-1} for the liquid, solution and gaseous states respectively[38].

d. Amide III vibration. This band appears between 1310 and 1290 cm^{-1} and is relatively weak in the infrared spectrum but the intensity ranges from very strong to strong in the Raman spectrum. Shifts in the band position are effected by the changing physical state and by deuteration thus demonstrating the contribution of nitrogen and hydrogen atoms to the vibration.

e. Other vibrations. Secondary amides also possess a characteristic band near 3100 cm^{-1} which has been described by Miyazawa[39] as the result of Fermi resonance of the nitrogen–hydrogen stretching mode with the combination band of the carbonyl stretching and nitrogen–hydrogen in-plane bending mode in *cis* amides. In *trans* amides the interaction occurs with the overtone of the amide I band.

3. Tertiary amides

There are no nitrogen–hydrogen bonds in tertiary amides and as a consequence there is an absence of vibrations associated with the group.

a. Amide I vibration. A single absorption band is observed in the 1650–1550 cm^{-1} region arising from the carbonyl stretching mode. In *N*,*N*-dialkyl-substituted amides the band occurs in the range 1670–1630 cm^{-1} as a strong band in the Raman spectrum[40]. Unlike the amide I band in primary and secondary amides the vibration is not particularly sensitive to changes in phase or solution concentration. However, polar solvents, capable of hydrogen bonding, cause noticeable changes in band position. In aromatic tertiary amides conjugation of the carbonyl group with the benzene ring produces a decrease in the amide I band wavenumber[41].

b. Other vibrations. The pseudo-symmetric stretching mode of the carbon–nitrogen–carbon fragment occurs as a strong to medium strength absorption in the wavenumber range 870–820 cm^{-1} in the Raman spectrum of amides of the type $HCONR_2$ and in the range 750–700 cm^{-1} for amides of the type $R^1CONR_2^2$. A further medium to weak band occurs in the Raman spectrum of *N*,*N*-substituted

formamides near 650 cm^{-1} and between 620 and 590 cm^{-1} in higher tertiary amides. The bands arise from the O···C···N in-plane deformations[40].

4. *Lactams*

The spectra of lactams in dilute solution are similar to those of the open-chain secondary amides in that a single band is observed near 3420 cm^{-1}. A second band of variable position occurs near 3200 cm^{-1} and is concentration-dependent[42].

The carbonyl stretching wavenumber is higher in the strained, five-membered rings than in larger rings. It also varies with solvent and physical state. In the four-membered ring butyrolactam the carbonyl absorption is observed at 1754 cm^{-1} in the vapour phase, whereas it occurs at 1680 cm^{-1} in the pure liquid, and at 1706 cm^{-1} as dilute solution in carbon tetrachloride[43].

The four-membered ring lactams or β-lactams have been extensively studied in the context of penicillin and its derivatives[44]. In simple β-lactams the carbonyl absorption is centred near 1780 ± 10 cm^{-1} whereas in penicillins it occurs near 1765 cm^{-1}.

Additional information on the infrared spectra has been reviewed by Bellamy[45,46] and the laser Raman data by Dollish and coworkers[47].

The spectra of *N*-vinyl lactams have been studied[48]. In the carbonyl stretching region two absorptions were observed, one attributed to the carbon–carbon double bond, the other to the carbonyl group. The carbonyl-group wavenumber is lowered to almost the same extent as in molecules containing the $>N-C=O$ bond system. Anomalies which exist in the intensities of the Raman bands of the carbonyl and carbon–carbon double bond serve to distinguish the *N*-vinyl lactams from molecules containing the $C=C-N<$ and $>N-C=O$ bond systems.

In a comprehensive concentration and solvent study of the nitrogen–hydrogen and carbonyl vibrational wavenumbers for the $n = 3 - 11$ lactams, $(CH_2)_nCONH$, Hallam and Jones[35,49] report several features which are discussed in terms of *cis*, *trans* and *skew* configurations of the peptide linkage. For dilute solutions of lactams in which $n = 3 - 5$ single nitrogen–hydrogen stretching absorptions are observed due to the amide group in the *cis* conformation. For the $n = 6$ lactam the band appears as a doublet which is attributed to planar *cis* conformations of the amide group. In the $n = 7$ lactam four different monomeric conformations are shown to coexist which are assigned to two *cis* and two *skew* conformations. The $n = 8$ lactam exhibits three bands which are assigned to two planar *trans* and one planar *cis* conformation of the amide group. The $n = 9 - 11$ lactams exhibit a doublet of bands which are attributed to two *trans* planar conformations of the amide group which, it is also suggested, arise from nitrogen–hydrogen groups inside and outside the ring. The observations closely parallel those recorded for the thio- and seleno-lactams[50].

The infrared and Raman spectra of δ-valerolactam (2-piperidone) and its *N*-deuterated derivative have been recorded for the liquid and solid (crystal at ambient and liquid nitrogen temperature) and solutions of varying concentrations in carbon tetrachloride and carbon disulphide[51]. The results indicate that δ-valerolactam in solution associates principally into cyclic dimers, whereas in the liquid state the dimer exists together with some oligomer chains. The liquid state behaviour is similar to that of 2-pyrrolidone and its *N*-deuterated derivative[52] which consists of a mixture of cyclic dimer and oligomer chains, but in the solid state it consists of cyclic dimers alone. The infrared and Raman spectra of α-chloro-δ-valerolactam (3-chloro-2-piperidone) have also been recorded[53].

The infrared spectrum of 2-pyrrolidone may be interpreted by assuming that the CONH group assumes a *cis* configuration by virtue of the ring structure. The high wavenumber of the nitrogen–hydrogen stretching mode of the gaseous monomer suggests that the ring is almost planar[29]. The dipole moment of 2-pyrrolidone[54] in dioxane solution at 30 °C (303 K) is 3.79 D a value which falls in the range 3.7–3.9 D recorded for simple amides as solutions in dioxane[55].

C. Nuclear Magnetic Resonance Spectra

The methodology of quantitative analysis employing n.m.r. spectroscopy has been described by Kasler[56]. A method based on n.m.r. and titrimetry has been described[57]. The method is based on the prior neutralization of an acidic or basic compound with a strong organic base or acid, respectively, which possesses a characteristic n.m.r. spectrum using an internal visual indicator. By recording the n.m.r. spectrum of the neutral mixture and measuring the integral ratio of the titrant to the remainder of the signals, the content of acidic or basic groups in the compound in terms of the other protons present in the molecule may be determined. As an example of the approach nicotinamide was titrated in solutions of 4 : 1 nitromethane–acetic anhydride with 3% 2,4,6-trinitrobenzenesulphonic acid in 9 : 1 acetic anhydride–acetic acid using methyl violet as indicator. The accuracy of titrant to titrated compound is claimed as usually within ±5%.

The p.m.r. method of quantitative analysis has also been applied to the determination of the amide and cyanide derived from nicotinic acid in binary mixtures dissolved in acetone containing 7% water as solvent[58].

Usually only one internal standard is employed during quantitative analysis. However, a technique has been described which involves the use of a pair of internal standards[59]. This, it is claimed, overcomes the limitations usually encountered during the use of a single internal standard.

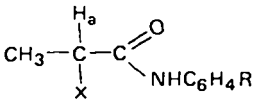
N.m.r. methods have been employed to great effect in the determination of configuration of *N*-substituted amides in particular, and in the calculation of the barrier to internal rotations. A high percentage of publications concerning the n.m.r. of amides is devoted solely to the latter.

An n.m.r. study of thirteen *N*-substituted aliphatic amides revealed that four substituted formamides exist in both the *cis* and *trans* configurations about the central carbon–nitrogen bond[48]. The *trans* form predominates but the percentage of *cis* isomer increases as the nitrogen substituent becomes more bulky in the sequence methyl, ethyl, isopropyl and *t*-butyl. Only the *trans* configuration was adopted by amides where the carbonyl substituent was larger than hydrogen. Small-ring lactams exist in the *cis* configuration[60] and a number of cyclic dimers of amides having a *cis* configuration have been reported including *N*-methyltrichloroacetamide[61].

Ma and Warnhoff[62a] report an n.m.r. method which attempts to improve the determination of *N*-alkyl groups, the estimation of which is usually made by the Herzig–Meyer method[62b]. The method depends on the decreased shielding of N(basic) methyl protons when the solvent is changed from deuterochloroform to perdeuteroacetic acid (or acetic acid) to trifluoroacetic acid. However, the shifts observed for amides and imines are very small and the method is not particularly useful.

Two half-amides of itaconic acid have been identified by a first-order analysis of their n.m.r. spectrum[63]. A method has been described whereby the enantiomeric purity of chiral amides may be calculated[64]. It is based on results obtained from a

study of the n.m.r. spectra of a series of chiral propionamides of type 7 determined in D(+)-1-phenylethylamine solution.



(7)

The proton-decoupled ^{15}N-n.m.r. spectra of amides are obtained with relative ease (notwithstanding the potential difficulties associated with the long ^{15}N relaxation times for these substances) when there is a directly bonded proton on the nitrogen and, sometimes, even in its absence[65]. The important factor is presumed to be the rate of proton chemical exchange from amide nitrogen.

The use of chemical-shift reagents is part of the n.m.r. method. The determination of the molecular geometry of a series of Eu(fod)$_3$ amide complexes has been discussed[66] [fod = tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) Eu(III)]. It is based on three assumptions:

(*i*) Only an average molecular geometry may be found for complexes in which several possible locations are available for the lanthanide. If only one preferred lanthanide site is assumed available in the complex the experimental data may approximately describe the geometry of the complex.
(*ii*) The conformation of the substrate should be rigid or should remain unaltered by the lanthanide addition.
(*iii*) In those circumstances under which conformational isomers exist which owe their identity to processes slow on the n.m.r. time-scale, lanthanide addition should not appreciably change their relative populations.

Quantitative analysis by n.m.r. spectroscopy has been applied to the determination of lactams. Kirchhoff and coworkers[67] report good agreement between results obtained by this method and by titration for a series of α-acyl lactams.

The chemical-shift non-equivalence of the diastereotopic protons at $C_{(4)}$ in identically 3,3-disubstituted β-lactams having an asymmetric carbon atom in positions ranging from β to ε of the chain attached to the nitrogen atom have been reported[68]. The non-equivalence is correlated to the nature of the substituents attached to the chiral centre and to its distance from the $C_{(4)}$ protons.

However, it is in the field of medicinal and biological chemistry that n.m.r. spectroscopy attains paramount importance. Casy[69] discusses the p.m.r. spectra of penicillin and cephalosporin derivatives, suggesting that the most informative signal is the doublet of doublets near δ 5.5 due to the β-lactam protons at $C_{(5)}$ and $C_{(6)}$ in benzyl penicillins and at $C_{(6)}$ and $C_{(7)}$ in cephalosporin derivatives. It is also suggested that, as the chemical-shift separations of the β-lactam protons in cephalosporin derivatives are in general greater than those of the penicillins this information may be used to distinguish the two classes of compounds.

In their investigations of simple β-lactam derivatives Barrow and Spotsweed[70] found that $^3J_{cis}$ (4.9–5.9 Hz) was consistently greater than $^3J_{trans}$ (2.2–2.5 Hz). On the basis of this information it was concluded that the β-lactam protons of penicillins are almost certainly *cis*-oriented unless fusion of the lactam to the thiazolidine ring drastically alters the shape of the four-membered ring[69].

D. Optical Activity

The phenomenon of optical activity has been known for many years[71,72]. The optical activity of a medium is attributed to the fact that the medium has different refractive indices for left and right circularly polarized radiation. Consequently, the velocity of left circularly polarized radiation is different from that of right circularly polarized radiation as they travel through the medium[73,74].

It is important to note that optical activity is exhibited by two classes of compounds: those in which the optical activity is evident in the crystal only and those in which the optical activity is exhibited by the solid and liquid in the pure state or as solution and by the gaseous state. The necessary condition for any molecule to exhibit optical activity is that it should be devoid of any centre of inversion, plane of symmetry or alternating rotation–reflection axis of symmetry[73].

The optical rotatory power of a pure substance, particularly in the liquid state, is generally expressed in terms of its specific (optical) rotation or specific (optical) rotatory power. The molar rotation, molar rotatory power (M) or molecular rotation (Φ) is obtained when the specific rotation is multiplied by the molecular mass M of the optically active material and the result divided by 100. This is generally accepted to be the most convenient unit, since comparison is then possible on a mole for mole basis[75]. Caution is necessary, however, since with the introduction of the Système Internationale (S.I.) units two sets of units are being used concurrently for the terms previously defined.

Right and left circularly polarized radiation is also differentially absorbed so that when an optically active medium interacts with plane-polarized radiation in the region of the spectrum in which an optically active chromophore absorbs, not only does the plane of polarization rotate but the resulting radiation is also elliptically polarized. The medium is then said to exhibit circular dichroism.

Optically active chromophores[76] may be classified into two extreme types[77]: (*a*) inherently dissymmetric chromophores, e.g. twisted biphenyls and skewed dienes, and (*b*) the inherently symmetric chromophores which are asymmetrically perturbed, e.g. the carbonyl group in esters, amides, lactones and lactams[78].

Problems may arise since it is possible that free rotation may occur in the molecules being studied. However, experiments have confirmed that rotamer composition is fairly constant or that one conformer is predominant irrespective of minor changes in the remainder of the molecule. Alternatively, changes in solvent may exert an appreciable influence even on rigid molecules and the presence of two Cotton effects, the sign of which depend on the solvent, would appear to be best explained in terms of solvation equilibria[79].

Choice of solvent depends on the nature of the chromophore under investigation. For low wavelength absorbing chromophores solvents with high ultraviolet penetration are required but unfortunately such solvents generally present solubility problems. Consequently, dioxane is often chosen as the solvent for optical rotatory dispersion (ORD) and circular dichroism (CD) studies[80].

The ORD curves of the thiocarbamates of α-amino acids exhibit very pronounced solvent effects[81]. *N*-Dithiocarbethoxy-L-alanine exhibits a positive Cotton effect in water, methanol, acetic acid, tetrahydrofuran and dioxane and a negative Cotton effect in chloroform and dichloromethane. In benzene or diethyl ether the material exhibits two CD maxima of opposite sign. Since the reversal of the sign of the Cotton effect appears to follow no general rule, caution should be exercised in the use of ORD and CD measurements for determining absolute configurations.

ORD and CD data are relatively sparse for lactams and particularly for amides. The few examples which are available for amides have been used to make comparisons with the corresponding carboxylic acids, most of them showing the same sign for the amide as for the carboxylic acid[82]. These data support the suggestion[83] that the $CONH_2$ function should behave optically in a manner essentially similar to COOH.

In an effort to rationalize optical measurements in peptide chemistry, attempts have been made to perform measurements on 'model compounds'. One such study involved L-3-aminopyrrolid-2-one in which the ORD curve was measured down to 220 nm[84]. The Cotton effect of the $n \rightarrow \pi^*$ transition, being positioned on the steep slope of a very much more pronounced negative Cotton effect (probably the $\pi \rightarrow \pi^*$), may be located only approximately and is assumed to be positioned near 230–235 nm. The Cotton effect curve shows a marked enhancement in dioxane solution relative to that in acetonitrile.

It has been suggested[84] that the $n \rightarrow \pi^*$ Cotton effect should follow a quadrant rule and that the $n \rightarrow \pi^*$ Cotton effect of a peptide group is a spectral feature which is enhanced by molecular rigidity, properly distributed vicinal atoms and a low effective dielectric permittivity. The ORD curve has also been suggested as being the multiple Cotton effect of a single peptide.

Wolf[85,86] in a comparison of lactone and lactam ORD and CD curves demonstrates their similarity, the essential difference being the shift of the lactam Cotton effect curves to shorter wavelengths. Klyne and Scopes[87] in a similar comparison of the CD data for pairs of corresponding lactones and lactams suggest that for some rigid compounds the CD maxima near 230 nm possess opposite signs. Data are scanty and in the few flexible systems for which information exists the lactone and lactam possess the same sign.

Weigang[88] has suggested a new sector rule for lactams. In it the chromophore is viewed along the bisectrix of the O=C—N angle and also from above, in projection on the lactam plane. The lactam group is considered as a perturbed modification of the carboxylate anion which possesses C_{2v} symmetry. The treatment considers the effects of various degrees of perturbation; for small perturbation a curved sector boundary exists, for moderate perturbation the boundary may close around itself and for infinite perturbation may even vanish yielding a quadrant rule[89].

Wolf[86] also cites an example of the analytical applicability of ORD curves under favourable conditions. The separation of certain lactam isomers may be monitored and criteria of purity assessed by measuring their ORD spectra, since the contamination of one isomer by another is easily detected if measurable differences in rotation exist between the extrema of the Cotton-effect curves.

In a more theoretical context, satisfactory qualitative agreement between calculated and experimental values for the rotational strength of the $n \rightarrow \pi^*$ transition in some simple γ-lactams using the CNDO–CI method have been reported[219].

E. Ultraviolet and Visible Spectra

Amides generally exhibit two absorption maxima: the $n \rightarrow \pi^*$ transition near 220 nm and the $\pi \rightarrow \pi^*$ transition near 190 nm, the latter being so intense that in many instances it obscures the relatively weak $n \rightarrow \pi^*$ transition. Thus the $n \rightarrow \pi^*$ transition occurs as an inflection at 220 nm in an aqueous solution of acetamide[90]. Generally open-chain amides are reported as absorbing below 220 nm[91]. The absorption near 190 nm is also subject to wavelength shifts when the solvent is changed from non-polar (hydrocarbon) to polar (water). Nielsen and Schellman[92]

recorded the spectra of sixteen amides of the type $R^1CONR^2R^3$ and concluded that there is, in general, a red-shift in changing the solvent from cyclohexane to water. The red-shift is large (~5 nm) in primary, small in secondary and negligible or reversed in tertiary amides. Substitution on the nitrogen atom causes strong red-shifts for λ_{max} in the series tertiary > secondary > primary. The oscillator strengths fall in the sequence primary < secondary < tertiary, and are greater in water than in cyclohexane in those instances where comparisons are possible. It was further observed that, when amides are placed in non-polar solvents such as cyclohexane or dioxane, the $n \rightarrow \pi^*$ transition occurs as a shoulder in the range 225–235 nm. The transition is not observed in aqueous solutions, because of the red-shift of the very intense $\pi \rightarrow \pi^*$ transition coupled with the blue-shift of the $n \rightarrow \pi^*$ band.

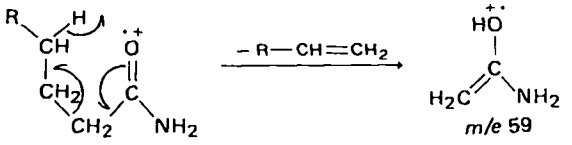
It is unfortunate that intensities are invariably quoted as ϵ_{max} or $\log \epsilon$ with no indication of the units although these are usually implied. It is important to regularly calibrate the absorbance scale of any ultraviolet/visible spectrophotometer or the ϵ values recorded may be inadvertently in error by considerable amounts. The use of S.I. units should be given serious consideration.

For a comprehensive selection of spectra, reference should be made to collections such as that edited by Perkampus[93].

The spectra of three α-lactams of type 8 (Section I.F) are characterized by well-defined maxima of low intensity[111]. The hypsochromic shift observed when the solvent changes from *n*-hexane to ethanol is characteristic of $n \rightarrow \pi^*$ transitions. In γ- and δ-lactones the transition occurs well below 220 nm and the only lactam to show absorption above 200 nm is *N*-methylpyrrolidone[54]. However, in five-membered ring *N*-acetyl lactams a peak was recorded at 217 nm and in six-membered ring *N*-acetyl lactams the peak occurred at 218 nm. In 2-pyrrolidone absorption occurs at 190 nm in aqueous and at 185 nm in cyclohexane solutions[92].

F. Mass Spectra

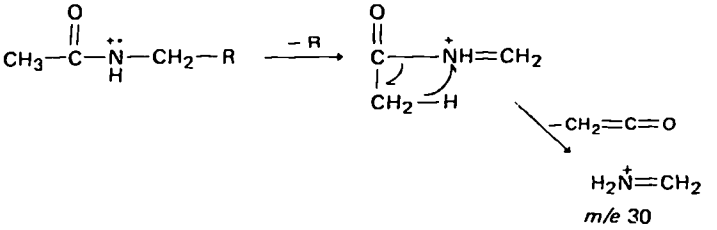
An early systematic study of the mass spectra of amides was made by Gilpin[94]. The spectra of thirtyfive aliphatic amides were tabulated, correlated and divided into three classes: primary, secondary and tertiary. In low molecular-mass primary amides an ion of *m/e* 44 is yielded from the process of α-cleavage and although β-cleavage does not occur, Gilpin[94] reported evidence of γ-cleavage. β-Cleavage is a major process when a three or more carbon-atom chain exists in the amide and the resulting transfer of a γ-hydrogen produces the intense peak at *m/e* 59 which characterizes the spectrum of these amides (equation 6). The spec-



(6)

trum of the only secondary amide with a γ-hydrogen in an alkyl chain attached to the carbonyl group recorded by Gilpin has a base peak at *m/e* 115. Secondary amides are also characterized by a double α- and carbon–nitrogen cleavage with accompanying hydrogen atom rearrangement[95]. Where there is no α-substitution adjacent to the nitrogen, secondary amides possess an intense peak at *m/e* 30 (CH_4N^+) which is, in many cases, the most intense peak in the spectrum. The peak

is attributed to cleavage of the nitrogen–carbonyl carbon bond and one of the carbon–carbon bonds β to the nitrogen atom accompanied by the rearrangement of a hydrogen to the nitrogen-containing portion of the molecule (equation 7). As this peak is also evident in the spectra of tertiary amides it has been suggested that the operative process closely parallels that observed in the secondary amide spectra[94,95].



(7)

The mass spectra of cycloalkyl amides are generally more complex than those of aliphatic amides[96].

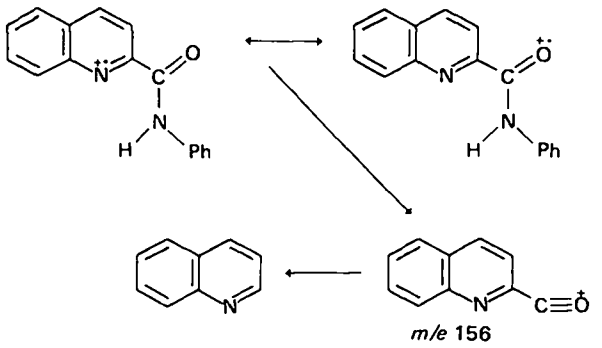
The fragmentation behaviour of aromatic amides is relatively simple. Acetanilide and benzamide have been investigated by Cotter[97] and may be considered typical examples. In acetanilide the base peak in the spectrum arises by expulsion of ketene from the molecular ion. The resulting fragment is, in mass, identical to aniline and the spectrum below *m/e* 93 closely parallels that of aniline, the major difference being evidenced by the much greater intensity of the *m/e* 77 ($C_6H_5^+$) peak in the secondary amide spectrum. Very similar behaviour has been observed in the spectrum of *N,N*-diphenylphenylacetamide and five of its homologues[98]. In these systems loss of phenylketene generates the base peak *m/e* 169 and the spectrum below this peak corresponds closely to that of diphenylamine.

Aryl migration in aryl amides during mass spectrometry has been investigated by Johnstone and coworkers[99] who found that the fragmentation of *N*-methyl-*N*-trifluoroacetylaniline proceeded normally with successive losses of CF_3 and carbon monoxide to yield the ion at *m/e* 106. However, the process is accompanied by another, involving rearrangement of the molecular ion, to give an ion at *m/e* 110, indicative of the elimination of a phenoxyl radical.

An investigation of the energy of activation for the rearrangement by trifluoroamides to trifluoroimino ethers[100] found that the rearrangement product required little energy to fragment (~0.05 eV as measured). The results correlated with the Brown σ^+ function and showed good linear plots for the *para*, but not for the *meta* substituents which fell on a different line. Separate plots of the ionization potential of the amides and the appearance potentials of the fragment ion showed similar linear correlations with the Brown σ^+ function, the *meta* and *para* substituents falling on different lines.

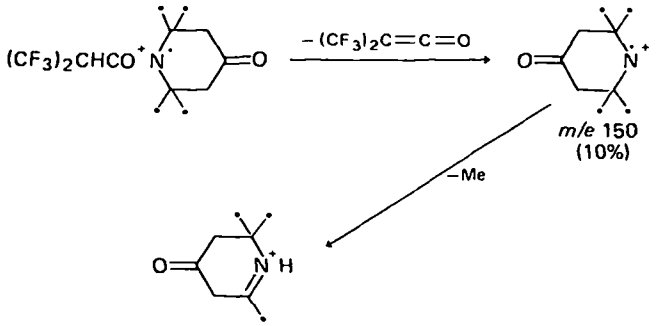
In the mass-spectrum fragmentation pattern of a series of derivatives of α-amino-α,α-diphenylacetamides[101] it was found that in all derivatives the most abundant fragments are ions resulting from α-cleavage.

In the mass-spectrum fragmentation of heterocyclic carbonamides the main ions are produced by cleavage of the amide bond followed by elimination of carbon monoxide[102]. The anilides of quinoline carboxylic acids (or quinaldic acids) expel C_6H_5N by migration of the amide hydrogen to the quinoline nitrogen followed by the elimination of carbon monoxide, the net result being regarded as the expulsion of phenyl isocyanate (equation 8).



(8)

The fragmentation behaviour under electron impact of certain tertiary amides, including 2-substituted *N*-acylaziridines and *N*-acylacetidines, has been determined for comparison[103]. The main degradation paths for the diisopropyl amides consist of cleavage α to the nitrogen atom preceded or succeeded by ketene elimination, or succeeded by olefin elimination. The main fragmentation paths for the amides may be described as, where possible, loss of ketene; if this is not possible then α-cleavage occurs as illustrated in equation (9) by the breakdown of the amide, the spectrum



(9)

of which is practically identical to the spectrum of the corresponding amine. When possible, however, loss of an olefin after α-cleavage may compete with ketene elimination. Finally intense peaks originating from hydrocarbon fragments are observed.

The low-energy mass spectrum of *N*-benzylacetamide[104] indicates that the major fragmentations of the molecular ion are similar to those observed in the acetanilide spectrum[97]. Major peaks are observed at *m/e* 149 (base peak), *m/e* 106 $[M-CH_3CO]^+$ and *m/e* 107 $[M-CH_2CO]^+$. When electron energies in excess of 18 eV are employed the $[M-CH_3CO]^+$ ion undergoes a secondary decomposition involving loss of hydrogen cyanide to yield the $C_6H_7^+$ ion.

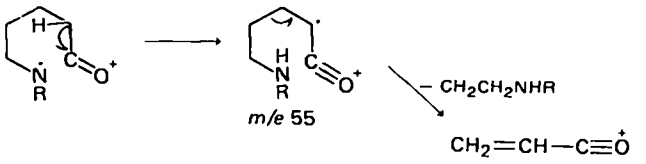
Using deuterium-labelled compounds Richter and Schwarz[105] have reinvestigated the elimination of methyl from amides of α,β-unsaturated carboxylic acids and suggest that the course of the reaction is more complex than had been assumed previously.

Amide–amide interaction analogous to, but weaker than, carboxyl–carboxyl interaction[106] has been observed in the mass spectra of maleic, fumaric, citraconic, mesaconic and itaconic diamides[107]. It is sufficiently marked to be of potential value as a structure-elucidating feature in the mass spectra of unknown compounds.

However, it appears that the intramolecular interaction of an amide function with an alkyl or methylene group is of relatively greater importance than amide–amide interaction.

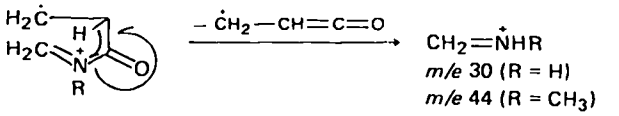
The simplest example of a saturated lactam is 2-pyrrolidone which, in spite of its relatively small size, exhibits a relatively complex mass spectrum[108]. A study of the mass spectra of 2-pyrrolidone, *N*-methyl-2-pyrrolidone, 2-piperidone and *N*-methyl-2-piperidone and their deuterated analogues has been reported by Duffield and coworkers[109]. The results are interpreted by assuming the intervention of molecular ions in which a non-bonding electron from either an oxygen or a nitrogen atom is removed by α-cleavage with or without hydrogen rearrangement. 2-pyrrolidone and 2-piperidone exhibit strong molecular ions which in the *N*-methylated compounds are markedly reduced in intensity. However, ions near *m/e* 40 are more abundant in the *N*-methyl analogues than in the parent lactams. The methyl group is not readily lost in any of the lactams. Loss of the fragment *m/e* 28 is achieved in *N*-methyl-2-pyrrolidone and 2-piperidone by expulsion of ethylene, whereas in *N*-methyl-2-piperidone there are contributions from carbon monoxide and CH_2N. In 2-pyrrolidone and 2-piperidone the *M*−29 species is generated mainly by elimination of $CH_2{=}NH$ and to a lesser degree by formyl and ethyl radicals while the *N*-methylated materials eliminate a formyl radical.

The two six-membered ring lactams possess an abundant fragment at *m/e* 55 arising in both cases by an identical process (equation 10). The base peak in



(10)

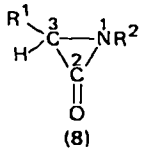
N-methyl-2-pyrrolidone, 2-pyrrolidone, 2-piperidone and *N*-methyl-2-piperidone and an abundant ion in 2-pyrrolidone arise from β-hydrogen transfer to nitrogen in the respective molecular ions with concomitant carbon–nitrogen bond fission as depicted in equation (11). The *M*−1 peak in 2-pyrrolidone arises by loss of the $C_{(5)}$



(11)

hydrogen atom. All four lactams have relatively intense *m/e* 42 peaks which possess variable composition. It is due almost entirely to the cyclopropane ion in 2-pyrrolidone, and in its *N*-methyl analogue to almost equal amounts of cyclopropane ion and the species $HC{\equiv}\dot{N}{-}CH_3$, *m/e* 42. In 2-piperidone the dominant fragment is cyclopropane ion, whilst in the *N*-methylated material the *m/e* 42 peak consists predominantly of ionized ketene $H_2C{=}C{=}O^+$ plus $HC{\equiv}\dot{N}{-}CH_3$ with a smaller contribution from the cyclopropane ion. The *m/e* 41 ion in all four lactams is predominantly the $C_3H_5^+$ species.

N-*n*-Butyl- and *N*-*n*-propyl-2-pyrrolidone display α,β-cleavage, and in the *n*-butyl homologue γ-cleavage, of the alkyl chain[110]. The base peak is formed from α-cleavage of the alkyl chain to nitrogen yielding *m/e* 98. Loss of 28 mass units is accomplished by elimination of carbon monoxide while no loss of ethylene is observed.



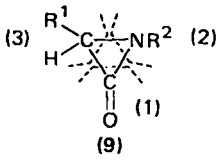
(8)

$R^1 = R^2$ = Adamant-1-yl (Ad = $C_{10}H_{15}$)

R^1 = Ad, R^2 = Bu-*t*

R^1 = Bu-*t*, R^2 = Ad

The mass spectra of three-membered ring lactams of the type 8 have been reported[111]. At 70 eV all three compounds exhibit weak or negligible peaks corresponding to the molecular ion 9 which possesses a marked tendency to lose



(9)

carbon monoxide [cleavage (1)]. In all the spectra the strongest peak above *m/e* 135 ($C_{10}H_{15}$) occurs at $M-28$ and this mode of fragmentation is important even at 10–12 eV. This pattern of behaviour is in marked contrast to that exhibited by β-lactams and their deuterated analogues[112]. There is practically negligible cleavage around line (2) whilst cleavage around line (3) becomes apparent when R^2 is adamantyl.

The mass spectra of 2-pyridones are adequately covered by Budzikiewicz, Djerassi and Williams[113].

G. Chromatography

Chromatographic methods have been employed extensively for the detection and determination of amides. The methods are not, however, without their pitfalls and a consideration of the possible sources of error should be examined. One such treatment is that outlined by Derge[114] in which the possible sources of error arising from sample preparation, sample introduction, the column, detection and the electronics of the detector are considered.

Several different reagents have been employed in the thin-layer chromatographic method when applied to amides. Substituted amides may be detected by a solution of dinitrophenylhydrazone followed by a solution of iodine[115]. Alternatively a method has been described for determining nicotinamide by means of 1-chloro-2,4-dinitrobenzene[116]. The standard deviation of the method is approximately ±10% and quantities of the order of 0.2 μg are capable of detection.

Long-chain acid amides are not easily determined by gas chromatography due to their high boiling point. However, if the column is treated with pyrophosphoric acid such amides can be determined by gas chromatography. Even so there are difficulties due to the limited solubility of the amides in most solvents[117].

Isomeric mixtures of carboxamido-substituted pyridines may be separated on an analytical scale by high-speed, high-resolution liquid chromatography yielding quantitative results with a standard deviation of approximately 1%[118]. It is also possible to make semiquantitative measurements down to 0.01% of an isomer within a substituent group. Isonicotinamide, nicotinamide and picolinamide may be resolved and estimated by this method.

Alkali-fusion gas chromatography employing potassium hydroxide containing approximately 1% of sodium acetate has been applied to amide groups and allows

conditions sufficiently drastic to force the reaction to completion. The end result is that chromatographic resolution and quantitation of the liberated ammonia or amines is possible. The method is rapid, specific and allows mixtures to be analysed. Primary, secondary and tertiary amides may be chromatographically analysed by this method and even polyamides are amenable to analysis using the alkali-fusion technique[119].

H. Polarographic and Titration Methods

Polarographic techniques have been applied to the amide systems, the bulk of the work being conducted in Russia and other Eastern European countries. A note of caution is necessary since in a few instances difficulties have been experienced with the names of the actual compounds involved.

A method based on the indirect polarographic determination of dimethyl formamide utilizes hydrolysis to dimethylamine which reacts with formaldehyde to yield a polarographically active product[120]. The sensitivity is 2×10^{-3} % and the maximum concentration capable of determination is 0.1%.

The effects of structure on the $E_{1/2}$ for the oxidation of the amide group in a number of *N*-substituted formamide derivatives reveals that $E_{1/2}$ lies between 1.92 and 2.10 V for substituted formamides, compared with 2.15 V for formamide. Comparisons with the reactivities of the formamides reveals that oxidation becomes more difficult as the electronegativity of the substituent decreases. The introduction of a C_3H_7 group shifts the $E_{1/2}$ of formamide in a positive direction by 60 mV relative to that produced by a methyl group. The C_4H_9 and C_5H_{11} groups shift the potential in the same direction by 100 and 120 mV respectively[121].

An examination of the polarographic reduction of the *ortho* and *para* derivatives of benzamide in aqueous and aqueous ethanolic solutions reveal that the observed half-wave potentials of the amide grouping correlate well with the nucleophilic substituent constants[122]. If the amide molecule contains other polarographically active groups (e.g. carboxylic acid, cyanide) the latter may be reduced if their reduction potential is reached before that of the amide group[123]. (The same remarks apply to *meta* benzamide derivatives). Reduction of the amide groups proceeds with rupture of the carbon–nitrogen σ bond, the presence of ammonia in the reduction products being taken as proof of the proposed mechanism.

The study has been extended by employing an aprotic medium, a 0.05 mol dm^{-3} solution of Et_4NI in dimethylformamide[124]. The $E_{1/2}$ values are more negative in dimethylformamide and the half-wave potentials all correlate well with nucleophilic substituent constants.

A non-aqueous titration method has been described for determining the higher lactams as solutions in acetic anhydride using perchloric acid[125]. It was observed that by measuring the half-neutralization potentials of the C_4–C_8 lactams there is a tendency for the basic properties to increase as the number of carbon atoms in the ring increases. Cyclic lactams containing more than nine carbon atoms have the amide groups in the *trans* position irrespective of the concentration of the solution. The results obtained with lauryl lactam suggest that the *trans* isomers do not conform to the *cis* isomer pattern.

II. LACTONES

A. Introduction and Miscellaneous

Lactones may be considered as internal esters and methods used for the determination of esters may be applied to the lactone function[126–128].

Lactones may be qualitatively and quantitatively determined by conversion to the corresponding hydroxamate with development of the red–violet colour formed with iron III ions (Section I.A). Lactones may be determined in presence of esters by their selective reaction[5]. A study of the kinetics of the formation of lactone hydroxamates has led to several mechanisms being proposed for the reaction[129]. The experimental procedure and reagents are identical to those employed for the determination of carboxylic acid anhydrides (Section III.A).

Glucono- and galactono-lactones may be estimated colorimetrically by measuring the colour intensity at 540 nm wavelength produced by the hydroxamate when reacted with iron III chloride in hydrochloric acid solution.

A microdetermination may be made by dissolving the sample in alcohol and treating it with a known quantity of 0.01 mol dm^{-3} sodium hydroxide solution at room or boiling temperature. The excess alkali is determined by titration with 0.01 mol dm^{-3} hydrochloric acid using phenolphthalein as indicator.

The identification and rough quantitative estimation of various types of lactone groups has been shown to be possible in all oxycelluloses using the rate-analysis study of reaction of acidic groups with potassium iodide–potassium iodate solution[130,131]. The method is slow since complete opening-up of all lactone groups takes in excess of 120 hours.

Relative configurational assignments have been made for some 2,4- and 2,3-disubstituted-γ-butyrolactones on the basis of stereoselective synthesis of their *cis* isomers[132]. Equilibrium studies on seven 2,4-disubstituted-γ-butyrolactones indicate that the differences in free energy (ΔG) between *cis* and *trans* isomers is small, the *cis* form being thermodynamically more stable than *trans* in all cases. However, the opposite is true for the 2-methyl-3-phenyl-γ-butyrolactones where the *trans* form predominates at equilibrium.

B. Infrared and Raman Spectra

The intramolecular ester of a hydroxy acid is a lactone and it consequently exhibits absorptions characteristic of an ester. However, the carboxyl stretching wavenumber is influenced by ring size, and the higher than normal ester wave number of the carbonyl stretching mode in four- and five-membered rings is attributed to changes in the hybridization or bond angle at the carbon atom in the carbonyl group. Thus for solutions of concentration less than 0.01% in carbon tetrachloride the corresponding wavenumbers (cm^{-1}) for the carbonyl stretching mode are[133]:

four-membered ring	1818
five-membered ring	1775
six-membered ring	1740
seven-membered ring	1727

The similarity of the unstrained ring lactones to open-chain esters is also evident in the dipole moment which is approximately 4.5 D for unstrained *s-cis* lactones[134].

The spectra of lactones are usually considered under the subdivisions: four-membered ring or β-lactones, five-membered ring or γ-lactones and six-membered ring or δ-lactones.

1. δ-Lactones

The wavenumber of the carbonyl stretching absorption occurs in approximately the same position as in open-chain esters[135,136]. However, most unsaturated five-

and six-membered ring lactones in which the double bond is conjugated to the carbonyl group exhibit two bands in the carbonyl stretching region in both the infrared and Raman[137]. The relative intensities of the two bands are independent of concentration, are very sensitive to the polarity of the solvent and vary reversibly with temperature. The splitting is attributed to an intramolecular vibration effect similar to that which occurs in cyclopentanone and in certain Δ^2-cyclopentenone derivatives. The existence of similar effects in other types of carbonyl compounds such as cyclic five-membered ring anhydrides indicates that caution is necessary if carbonyl splitting of this kind is to be distinguished from that associated with equilibria between conformational isomers.

2. γ-Lactones

The carbonyl stretching wavenumber in saturated γ-lactones is approximately 35–40 cm^{-1} higher than δ-lactones[138,139]. Saturated five-membered ring γ-lactones generally exhibit one band near 1770 cm^{-1} whereas α,β-unsaturated γ-lactones[137] generally exhibit two bands of unequal intensity and separated by approximately 30 cm^{-1}. The spectra of γ-lactones have been extensively studied[140] and in general γ-lactones absorb in the range 1775–1790 cm^{-1} in carbon tetrachloride solution, 1770–1785 cm^{-1} in chloroform solution and near 1770 cm^{-1} in the solid state. These results indicate that the nature of the solvent and the physical state of the material have little influence upon the band wave number. The Raman spectrum of γ-butyrolactone has been reported[141].

A detailed study of the infrared spectra of eight endocyclic conjugated γ-lactones reveals an absorption in the region 770–750 cm^{-1} which is in marked contrast to the spectra of γ-lactones with an exocyclic double bond[142].

3. β-Lactones

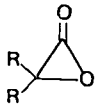
As previously mentioned, the carbonyl stretching wavenumber is of the order of 100 cm^{-1} higher in β-lactones than in δ-lactones[143,144]. A complete vibrational analysis based on the infrared and Raman spectra of β-propiolactone[145] indicates that the carbonyl stretching mode occurs in the infrared spectrum at 1882 cm^{-1} in the vapour, 1832 cm^{-1} in the pure liquid and at 1830 cm^{-1} in the Raman of the pure liquid. In β-butyrolactone[146] the carbonyl stretching mode, in the infrared spectrum, occurs at 1861 cm^{-1} in the vapour and at 1823 cm^{-1} in the pure liquid.

The tendency to become involved in hydrogen bonding is less in β-lactones, than in γ-lactones, than in δ-lactones if measured by the shift $\Delta\nu$ of the carbonyl stretching mode as the solvent is changed from carbon tetrachloride to methanol[147]. For β-propiolactone[133] $\Delta\nu$ = 7 cm^{-1}, for β-lactones[147] $\Delta\nu$ = 12 cm^{-1} and for β-lactones[147] $\Delta\nu$ = 15 cm^{-1}.

4. α-Lactones

The preparation of α-lactones (3-membered ring) is normally difficult but an easy, high-yield photochemical synthesis of α-lactones under conditions which permit infrared spectroscopic observation has been reported[148]. The α-lactone **10** (R = n-C_4H_9), exhibits a carbonyl stretching mode at 1895 cm^{-1} recorded as a liquid nitrogen-cooled glass.

INDO calculations on acetolactone and its difluoro and dimethyl derivatives indicate that in all cases the closed α-lactone system is more stable than the open-ring forms[149].

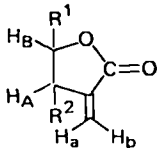


(10)

C. Nuclear Magnetic Resonance Spectra

The theory and application of quantitative analysis by n.m.r. spectroscopy has been discussed by Kasler[56]. The technique has been applied more specifically by Kirchhoff and coworkers[67] to 22 α-acyl lactones, lactams and thiolactones. The agreement between their results and those obtained by titration methods was reported as good.

The determination of the stereochemistry of five-membered α,β-unsaturated lactones (**11**) possing an exomethylene double bond based on the allylic long-range couplings of the exomethylene protons has been reported[150]. The allylic couplings *transoid* ($^4J_{b,A}$) and *cisoid* ($^4J_{a,A}$) are employed in the solution of the problem which is based on the X-ray data of Asher and Sim[151] which demonstrate that the resonance structure, $-\bar{O}=(C\cdots\bar{O})-$, contributes appreciably to the ground state of the lactone group. In the case of the lactone **11** the structure may be stabilized by



(11)

conjugation with the exomethylene double bond. As a result it is anticipated that the conjugation will appreciably limit the conformational mobility of the γ-lactone ring and consequently limit the variability of the allylic dihedral angle ϕ, which is the dominant factor in the determination of the magnitude of the allylic coupling. On the basis of a comparison between a large number of published and unpublished p.m.r. data for sesquiterpene lactones of type **11** two rules have been formulated:

(*i*) *trans*-lactones of type **11** have larger $|^4J_{cisoid}|$ and $|^4J_{transoid}|$ than *cis* lactones,

(*ii*) $|^4J_{trans}| \geqslant 3\ \text{Hz} \geqslant |^4J_{cis}|$.

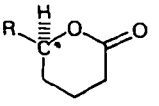
However, it is suggested that further careful work is required.

D. Optical Activity

Early optical rotation measurements of lactones were confined to monochromatic measurements or to the region of the spectrum of the plain ORD curves[152], the rotation values of which are largely determined by the sign and amplitude value of the Cotton effect curves at shorter and, at that time, inaccessible wavelengths. The optical rotation of the lactone was related to the configuration of the carbon atom carrying the potential hydroxyl group by Hudson's rule[153,154].

The lactone rule of rotation is a qualitative expression correlating the sign of rotation with the stereoconfiguration of the γ-lactone ring, but the magnitude of the rotation is not disclosed. In γ- and δ-sugar lactones the stereochemistry of the

carbon atom carrying the potential hydroxyl group determines the sign of the rotation contribution of the lactone ring. Hudson's rule has been explained by Klyne and coworkers[155]. If the hydrogen atom at the alkoxy carbon (C*) in **12** and **13** lies below the plane of the lactone ring then the rotation difference



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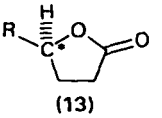


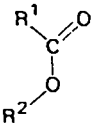
(13)

(Δ value) will be positive and the compound is dextrorotatory. Conversely, if the hydrogen atom lies above the plane of the ring, the compound will have a negative Δ value. In the case of a complex lactone with several asymmetric centres, each centre contributes to the total rotation of the molecule. Consequently in order to consider only that part of the total rotation which is due to the lactone function, it is necessary to subtract from the lactone rotation, the rotation of a suitable reference compound containing all the same asymmetric centres as the parent compound but without a lactone ring.

Hudson's original rule was later extended[156] to include compounds in which the lactone group is fused to other alicyclic rings. Many applications of the extended Hudson rule have been made, exceptions have been noted and certain limitations have been suggested[155]. Although the extended Hudson rule permits conclusions to be drawn regarding the stereochemistry of a single asymmetric centre in a limited range of optically active lactones, i.e. those in which the alkoxy carbon atom is asymmetric, it does not apply to any other type of optically active lactone in which the alkoxy carbon atom is not asymmetric.

Hudson's rule is also complemented by the rule, formulated by Okuda and coworkers[157], which states that when a hydroxyl group situated on the carbon atom adjacent to the carbonyl function of the γ-lactone ring has the (*S*) configuration according to the Cahn–Ingold–Prelog convention[158] the Cotton effect associated with the weak $n \rightarrow \pi^*$ transition around 220–230 nm will be positive. Conversely a negative Cotton effect is associated with a secondary alcohol group in such a situation presenting the (*R*) configuration.

One of the major advantages of studying lactones is that they are rigidified or frozen esters and that they are a group of known conformation. The ester function is approximately planar and may exist in the *s-cis* and *s-trans* conformations, **14** and **15**, respectively. Dipole-moment measurements[159] indicate that the favoured conformation of acyclic esters is *s-trans*.



s-cis

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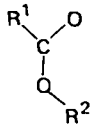


s-trans

(15)

Lactones are examples of esters possessing the *s-cis* conformation and only when the ester function is incorporated into a ring of eight or fewer members does the less favourable *s-cis* conformation appear.

The $n \rightarrow \pi^*$ transition responsible for the lactone Cotton effect has been studied spectroscopically[160]. Propiolactone in isooctane exhibits λ_{max} at a wavelength of

207.2 nm whereas for butyrolactone in isooctane the $n \rightarrow \pi^*$ transition occurs at 214.0 nm. The relatively high energy transition in propiolactone is probably due to bond-angle strain in the four-membered ring. The relatively low energy transition in butyrolactone probably indicates that the unstrained *s-cis* conformation has its $n \rightarrow \pi^*$ absorption located at longer wavelength than the *s-trans* form but a five-membered ring lactone still possesses some internal strain as evidenced by its higher than normal carbonyl stretching wave number (1783 cm^{-1} in carbon tetrachloride solution)[147]. The abnormally high carbonyl stretching wave number in butyrolactone (1841 cm^{-1} in carbon tetrachloride solution) has been attributed to the increase of *s*-character in the σ-bond of the carbonyl group as the internal angles are reduced which in turn should shorten both the σ and the π bond. It has also been observed that, in their ability to hydrogen-bond to methanol-d_1, lactones and cyclic ketones are approximately equal and their basicities both lie in the order 6 > 5 > 4-membered ring. As it is the carbonyl oxygen and not the ether oxygen of the lactone which is involved in hydrogen bonding it is suggested that the $n \rightarrow \pi^*$ transition of lactones would have the same solvent sensitivity as cyclic ketones.

A major impetus was given to the study of optical activity by the development of the octant rule[161], in that it relates the sign and amplitude of the Cotton effect exhibited by an optically active ketone to the spatial orientation of the atoms about the carbonyl function. The symmetry planes of the orbitals involved in the $n \rightarrow \pi^*$ transition are used as a frame of reference for considering the asymmetry of the compound.

It was directly as a result of studying lactones that Klyne and Scopes[162] proposed the lactone sector rule which is formally derived from the octant rule. The lactone group is roughly planar and each of the carbon–oxygen bonds in the lactone group is considered to possess a proportion of double-bond character. In the absence of evidence to the contrary regarding the proportions of the two canonical forms **16** and **17**, it may be assumed that the two carbon–oxygen bonds

(16) (17)

are equivalent and that the plane bisecting the carboxyl angle may be regarded as a symmetry plane. Klyne and Scopes[162] recognized that it is conceivable that the nodal surfaces may be non-planar and that the vertical surface does not bisect the carboxyl angle, but to a first approximation the treatment allows the signs of the contributions made by the alkyl groups and cycloalkane rings attached in various positions to the lactone group to be rationalized.

The space around the lactone group may be divided into sectors by means of planes meeting at the carboxyl carbon and the signs used in the ketone octant rule[161] must be reversed for lactone sectors[163]. Consequently atoms lying in the back upper right and lower left sectors make positive contributions to the lactone Cotton effect whilst atoms in the back upper left and lower right sectors make positive contributions.

It is necessary to consider two views of each molecule in order to predict the sign of its Cotton effect from the lactone sector rule[163]. These are the view along the bisectrix of the O–C–O angle (the usual octant projection) and the view of the molecule from above projected onto the plane of the lactone ring. Since the lactone group lies in a true symmetry plane the signs of the back lower sectors are

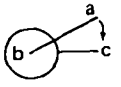
necessarily opposite to those of the upper sectors. Compounds in which the lactone ring is a terminal six-membered ring could possibly, subject to the absence of any additional constraints tending to introduce rigidity into the ring, take up a half-chair, half-boat or intermediate conformation. Jennings and coworkers[163] base their drawings on the half-boat conformation in the cases considered but suggest that the shape of the molecule with reference to the lactone chromophore is not very greatly altered when the half-chair form is used.

As a further test of its applicability the lactone sector rule has been applied semiquantitatively to eleven lactones where the lactone group bridges a carbocyclic ring[164]. The predictions were experimentally verified with no exceptions and were taken to confirm that it is the immediate environment of a chromophore which has the greatest effect on, and in many cases determines, the sign of the Cotton effect.

On the basis of these and other results, Klyne and coworkers[155] concluded that the lactone sector rule may be applied to any type of lactone, not only those with an asymmetric alkoxy carbon atom and may therefore be assumed to have a more general application than Hudson's rule even though it is much more difficult to apply.

The sign of the Cotton effect and the conformation of the δ-lactone ring has been thoroughly investigated by Wolf[165] who has also recorded the ORD and CD spectra of several lactones and lactams[85,166]. The rule which Wolf formulated as a result of these studies has been simplified and extended to lactones with five- and seven-membered rings by Legrand and Bucourt[167]. The rules formulated by Legrand and Bucourt form the basis of the determination of the absolute configuration of the lactones (+)5-decanolide (tetrahydro-6-pentyl-2*H*-pyran-2-one) and (+)5-dodecanolide (tetrahydro-6-heptyl-2*H*-pyran-2-one) from ORD and CD measurements[168]. The following parts of the rules were important to the study:

(*i*) A dihedral angle formed by three bonds a, b and c is labelled positive (**18**) when in the Newman projection the front bond, a, has to be rotated clockwise to place it on the back bond, c. In the reverse case (**19**) the angle is labelled negative.



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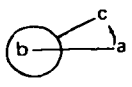
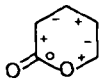


(19)

(*ii*) The dihedral angles formed by the sides of a cyclic molecule have a characteristic sequence of signs for each conformation demonstrated for the half-chair and the boat conformation in **20** and **21**, respectively (the antipodes have opposite signs).



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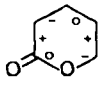
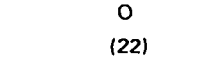


(21)

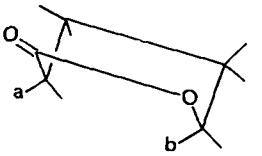
(*iii*) The sign of the Cotton effect of the lactone chromophore is opposite to that of the dihedral angle between $C^1C^2C^3$ and $C^2C^3O^4$ in the system **22**.



(22)

The ultraviolet absorption spectra of the two lactones studied exhibit an absorption maximum at 221 nm in hexane. The CD spectrum, on the other hand, exhibits two bands, one positive near 210 nm and one negative near 240 nm. Such a 'double-humped' curve with a separation between the maxima of approximately 30 nm is characteristic of two overlapping bands possessing opposite signs and separated by a few nanometres. The two cotton effects of the CD spectra were both discernible in the ORD curves.

The two bands in the CD spectrum of a δ-lactone have been ascribed[165] to the boat conformation (λ_{max} below 225 nm) and the half-chair conformation (λ_{max} above 230 nm). It is usually assumed that a δ-lactone normally takes up the boat conformation (23) with a planar lactone group[165]. When the lactone is substituted in position a and/or b, 1,4 interactions that may force the molecule into the half-chair conformation (24) arise. The δ-lactones of Korver's study[168] have alkyl



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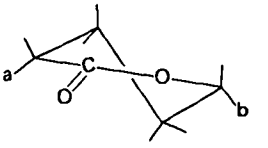
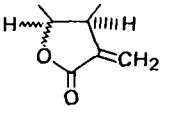


(24)

groups in the b position and the two bands in the CD spectrum of the lactones reflect the presence of both the boat and half-chair conformations. The presence of the conformational equilibrium is confirmed by the solvent-dependency of the CD spectrum and the low-temperature CD measurements.

There are two conclusions to be drawn from these latter data. The half-chair conformation is more stable than the boat conformation in 5-decanolide and at −185 °C (88 K) the conformational equilibrium has shifted completely to the side of the half-chair conformation. The presence of the positive band of the boat conformation at slightly lower wavelength produces a red-shift in the negative maximum at temperatures above −185 °C (88 K).

A large number of sesquiterpene lactones contain the α-methylene-γ-lactone chromophore (25) which gives rise to a maximum in the CD curve in the range 246–261 nm.



(25)

The correlation of the sign of the Cotton effect and the position and stereochemistry of the lactone ring fusion has been summarized by Stöcklin and coworkers[169]:

Position \ Ring fusion	*cis*	*trans*
$C_{(6)}$	+	−
$C_{(8)}$	−	+

The conclusions are based on the data for 44 lactones and only a few compounds are not consistent with the rule.

Klyne and Scopes[170] have given a review of the situation of the lactone sector and related rules. Complete rationalization is impeded by the lack of reliable information and understanding of the transitions involved in the absorption of lactone groups in the region 190–220 nm and by a paucity of detailed knowledge concerning the preferred conformations of even six-membered ring lactones in solution.

E. Ultraviolet and Visible Spectra

The spectra of many lactones are recorded concurrently with ORD/CD measurements. Closson and Haug[160] report λ_{max} for the $n \rightarrow \pi^*$ transition in propiolactone and butyrolactone (Section II.D). This transition occurs near 220 nm in campholide[171] (near 225 nm for solution in *n*-hexane and near 218 nm for solution in trifluoroethanol) and near 217 nm in γ-lactones of aldonic and related acids[172,173] (~0.01 mol dm^{-3} aqueous solution).

Although there is decreased strain in six-membered ring lactones little movement of the $n \rightarrow \pi^*$ transition to relatively longer wavelength is observed. In δ-valerolactone the absorption occurs at 214 nm (aqueous solution). Supporting evidence is to be found in a comprehensive study of the $n \rightarrow \pi^*$ transition of a series of saturated lactones varying in ring-size from six to seventeen members[174]. The solvents employed included isooctane, acetonitrile, methanol, ethanol and 2,2,3,3-tetrafluoropropanol.

F. Mass Spectra

Only a small fraction of the total current is carried by the molecular ion and it has been suggested[175] that the best criterion for the molecular size of an unknown lactone is often the gas-chromatographic retention time. An important feature in the mass spectra of lactones of general formula 26 and 27 arises from loss of the

R = saturated alkyl

(26) (27)

side-chain by cleavage adjacent to oxygen to yield *m/e* 85 and *m/e* 99 from γ- and δ-lactones respectively[176], and readily characterizes the number of carbon atoms in the lactone ring. The structure of lactones with larger rings may be identified by this rule.

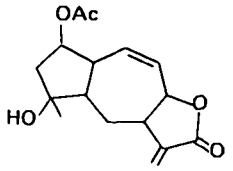
As the chain length increases from hydrogen or methyl to three or more carbon atoms loss of water becomes significant and it is presumed that at this chain length a steric configuration is permitted that is favourable to the transfer of a hydrogen atom. The transfer having been accomplished, the lactone ring is assumed to lose stability allowing additional hydrogen transfer and subsequent loss of water. As the chain length increases ions formed by the loss of a second water molecule also occur. For smaller γ-lactones[176] it has been established that the ion *m/e* 28 is primarily due to $C_2H_4^+$ from the lactone ring. A loss of 44 mass units in smaller

lactones is attributed to the loss of carbon dioxide but it is insignificant for lactones containing more than seven or eight carbon atoms.

The ω-lactone, cyclopentadecanolide, exhibits several unexpected rearrangement peaks in its mass spectrum[176]. Significant ions at *m/e* 222 and 204 ($M-18$ and $M-36$ respectively) indicate that the ring is readily broken in the excited parent ion, permitting a transfer of hydrogen from hydrocarbon portions to the oxygen atoms and resulting in the observed loss of one and/or two water molecules. An ion of *m/e* 180 ($M-60$), unusual for a lactone system, is presumed to arise by rearrangement, resulting in a loss equivalent to an acetic acid molecule and the formation of the ion $C_{13}H_{24}^+$. This ion apparently loses a molecule of hydrogen to yield $C_{13}H_{22}^+$ at *m/e* 178.

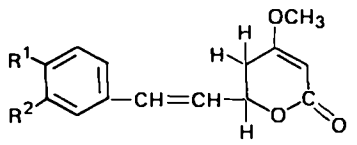
In the case of δ-lactones a pair of peaks at *m/e* 70 and 71 and a peak at *m/e* 42 are useful for characterization purposes[175].

The elucidation of the structure and the mass spectrum of the cytotoxic sesquiterpene lactone gaillardin (28) and several of its derivatives has been described[177]. Unlike other sesquiterpene systems the expulsion of the entire lactone ring is of minor importance. The determination of the structure of the sesquiterpene lactone vernolide using mass spectrometry has also been reported[178].



(28)

The mass spectra of kawa lactones differ markedly according to their degree of hydrogenation[179]. An unexpected fragmentation occurs in the kawaine-type lactone **29**, where a fragment arises which corresponds to cleavage at the position of the carbon–carbon double bond.



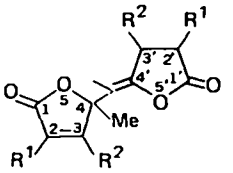
(29)

Some δ-lactones, substituted in various positions by methyl groups, have been investigated by Millard[180]. Only for monosubstituted lactones was the loss of carbon dioxide important. However, a fragmentation mode common to all the lactones studied is elimination of the ring oxygen atom plus the adjacent carbon atom with its substituents as a neutral carbonyl molecule.

A common feature in the mass spectra of santonins is the appearance of an ion at $M-73$ which is attributed to the elimination of $C_3H_5O_2$ regarded as expulsion of the γ-lactone ring plus one additional hydrogen atom[175].

The fragments eliminated by three bicyclic γ-lactones differ and indicate that the expulsion of a methyl radical, carbon monoxide and ketene are important processes[181].

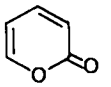
Consecutive carbon monoxide eliminations have been observed[182] in the mass spectra of the two α,β-unsaturated γ-dilactones **30** and **31**. There is also strong evidence that the fragment C_2O_2 is ejected. The molecular ion of **31**, as expected, is more intense due to higher alkylation at the double bonds.



(30) R^1 = Me, R^2 = H

(31) R^1 = R^2 = Me

The mass spectra of 2-pyrone (**32**) and other pyrones are summarized by Budzikiewicz and coworkers[183].



(32)

G. Chromatography

Chromatographic techniques have been applied to the qualitative and quantitative analysis of lactone systems. The detection of unstable lactones using thin-layer chromatography and the iron III hydroxamate test has been described[184]. The spray reagents consisted of an alkaline solution of hydroxylamine and an acidic solution of ferric chloride. Seven solvent systems were examined and the purple-brown hydroxamate spots appeared after approximately fifteen minutes or more. The colour of the spots originating from the unstable lactones became more distinct after some hours, but simultaneously interfering compounds also developed and became visible. In the absence of interferences the results, when read some hours after spraying, indicated detection limits for the unstable lactones of approximately 2 μg. For readings taken on the original colour development the detection limit was approximately 4 μg.

The thin-layer technique has also been applied to the separation of sesquiterpene lactones from *Geigeria aspera* and *Geigeria filafolia*[185]. Three different solvent systems were employed all of which were useful for identifying vermeerin, which is relatively difficult to colour. Reagents containing strong mineral acids were found to be the most suitable.

In a more applied context lactones in Cheddar cheese have been determined by a simple column extraction technique followed by gas chromatography of the cheese extract[186]. γ-C_{12}, δ-C_{10}, C_{12} and C_{14} lactones were detected easily and quantitatively by this method which is based on a flavour extraction technique modified to extract specifically lactones which are subsequently identified by gas chromatography.

III. ANHYDRIDES

A. Introduction and Miscellaneous

With the exception of formic acid, which on dehydration yields carbon monoxide, carboxylic acids form anhydrides in which water is eliminated between two

molecules of the acid. Carboxylic acid anhydrides are, in general, very reactive and are often involved in many of the reactions that are undergone by their parent acids. Consequently any reaction that is used for the determination of an anhydride must not occur with the free acid to any practical extent during the continuance of the determination.

Acid anhydrides are comparatively stable to water. However, hydrolysis occurs more rapidly with warm water or by heating with aqueous alkali.

The analytical procedures applicable to acid anhydrides have been reviewed by Hammond[187] and Cheronis and Ma[188]. Certain macroprocedures are not readily adapted to the microscale. These include[188]: (i) methods based on hydrolysis and measurement of unreacted water, (ii) methods based on anilide formation and titration of the carboxylic acid formed, and (iii) methods based on measurement of heat of reaction on hydrolysis or anilide formation. It is conceivable that the latter method is amenable to microcalorimetric procedures but little evidence exists. The following methods are applicable to micro and semimicro determinations[188].

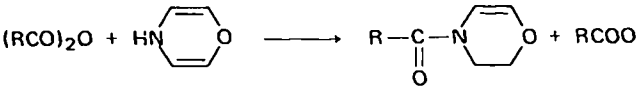
An acid anhydride dissolved in an organic solvent and titrated with sodium methoxide in methanol/benzene mixture reacts as a monobasic acid (equation 12).

$$(RCO)_2O + NaOMe \longrightarrow RCOOMe + RCOONa \qquad (12)$$

Thymol blue is a suitable indicator. In a 1 : 1 pyridine–water mixture the pyridine acts as a catalyst for the hydrolysis of the anhydride function to two carboxyl groups provided that no alcohol is present. After adding the sample and mixing at room temperature the solution is immediately titrated with aqueous sodium hydroxide (equation 13). Trimethylbenzylammonium hydroxide in pyridine containing a small amount of water has been used as a titrant.

$$(RCO)_2O + 2\,NaOH \longrightarrow 2\,RCOONa + H_2O \qquad (13)$$

Carboxylic acid anhydrides react quantitatively with morpholine in methanol solution (equation 14)[199]. The method is rapid since reaction is completed at room



(14)

temperature in 5–10 minutes. The unreacted morpholine is determined by titration with standard methanolic hydrochloric acid. Various mixed indicators may be employed of which methyl yellow/methyl blue and bromocresol green/methyl red are typical examples. It should be noted that methyl yellow (4-methylaminoazobenzene) has been termed a carcinogen and although the use of a 1% solution is permissible extreme caution should be exercised. Ruch[189] has reported that 4,4′-bis(4-amino-1-naphthylazo)-2,2′-stilbenedisulphonic acid is superior to methyl yellow visually as well as in matching the equivalence points of both blank and sample in the morpholine methods for determining carboxylic acid anhydrides. The method is not applicable to anhydrides whose parent acids have ionization constants in water of greater than 2×10^{-2} (for example malic and citraconic anhydrides) because the free organic acids are acidic to the indicator. Obviously any compound which reacts with morpholine must interfere.

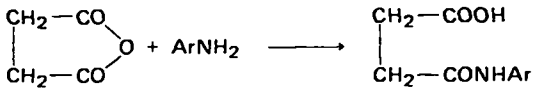
The morpholine method for determining anhydrides has been applied in modified form to the quantitative estimation of stearic anhydride in isopropenyl stearate[200]. It consists of reacting the anhydride with morpholine and back-titrating the unreacted morpholine with methanolic hydrochloric acid. Ketene,

diketene and acid chlorides may interfere and mineral acids certainly interfere. If the interference is quantitative appropriate corrections may be applied. The estimation is unaffected by isopropenyl stearate or stearic acid in the concentration range 0–10% of stearic anhydride.

The reaction of acid anhydrides with aniline to form an equimolar quantity of the corresponding anilide has been used in quantitative estimations (equation 15).

$$(RCO)_2O + ArNH_2 \longrightarrow RCONHAr + RCOOH \qquad (15)$$

The excess aniline is back-titrated with standard 0.2 mol dm^{-3} hydrochloric acid in ethylene glycol/isopropanol mixtures or with standard 0.1 mol dm^{-3} perchloric acid in glacial acetic acid. Substituted anilines have been employed to overcome the complications arising from the combination of aniline with liberated free acid. When the cyclic anhydrides of dibasic acids such as succinic or phthalic acids are used the reaction is of similar type except that the primary product is an amido acid (equation 16). Since the product of this reaction of a cyclic anhydride with an



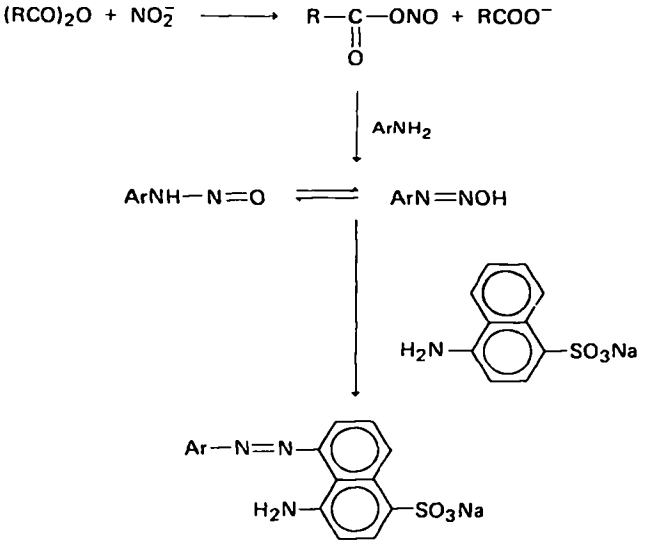
(16)

aryl amine is usually crystalline it has long been used for characterization purposes. Furthermore, the products are converted into anils by heating at temperatures above their melting point[190,191].

The reaction of acid anhydrides with anhydrous oxalic acid in dry pyridine liberates carbon monoxide and carbon dioxide (equation 17). The evolved mixed

$$(RCO)_2O + (COOH)_2 \longrightarrow 2\,RCOOH + CO + CO_2 \qquad (17)$$

gases may be determined gasometrically or the carbon dioxide gravimetrically by passage of the gas through an absorption tube containing Ascarite. Water must be rigorously excluded for the method to be successful.



(18)

Certain aromatic amines react with a mixture of acid anhydride and nitrite to form diazotates which, when coupled with alkaline aminonaphtholsulphonic acid, yield intense, water soluble, dyes (equation 18).

Acid anhydrides may be qualitatively and quantitatively estimated by the hydroxamic acid formed from their reaction with hydroxylamine in alkaline solution[5]. The sample, which is usually dissolved in benzene, is heated with alkaline hydroxylamine for ten minutes and when cool is treated with acidic ferric perchlorate solution. The calibration curve for quantitative estimations should be prepared from the pure anhydride as the wavelength of the absorption maximum may vary with individual compounds. Phthalic anhydrides which are insoluble in benzene may be dissolved in peroxide-free tetrahydrofuran.

Because of this selective reaction anhydrides may be determined in the presence of esters by this method. For anhydrides alone the accuracy of the method is reported as ± 2% but for mixtures it is less accurate. Acids, most amides and nitrites do not interfere[5]. The method has been applied to the estimation of acetic anhydride in the atmosphere[192], and phthalic anhydride may be estimated photometrically[14].

Spot tests for the identification of the anhydride function have been described by Feigl and Anger[193]. Légrádi[194] suggests a spot-test method for the detection of acid anhydrides that is based on the observation that *o*-nitrophenylhydrazine yields an acid–base indicator with anhydrides. In an alkaline environment the product yields a violet to blue colour and since the reagent is not an acid–base indicator it does not interfere with the test. Acid chlorides and some oxo compounds respond to the test, but acid amides, imides, esters, sulphamides and peroxides do not. In some instances it is possible to detect anhydrides in the presence of acids, for example 0.01% acetic anhydride in acetic acid.

A method for the quantitative estimation of acid anhydrides (and acylating agents) has been described which is based on the development of the blue luminescence which occurs when acylating agents are reacted with isonitrosoacetanthranilic acid (2-carboxyisonitrosoacetanilide) and irradiated with ultraviolet radiation[195]. It is claimed that the quantitative determination of not less than 1×10^{-11} mol of acid chloride and 1×10^{-12} mol acid anhydride in 2 cm^3 of solution is possible and that it is possible to detect qualitatively 1×10^{-12} and 1×10^{-13} respectively in the same volume. The sensitivity of the luminescent method may be improved by a factor of ten or more if the submicro amounts of acid chloride and anhydride have been concentrated by crystallization concentration (zone freezing) of their solutions[196].

The quantitative determination of acid anhydrides may be accomplished by a thermometric method, for the principles of which the reader is referred to the monograph by Bark and Bark[197]. The method may be applied to the estimation of anhydrides alone or in the presence of the parent acid. In most instances the presence of large amounts of parent acid has no effect on the determination and for 0.5 mmol of anhydride the accuracy is approximately ± 1%[198].

B. Infrared and Raman Spectra

Resonance within the anhydride function is sufficient to hold the group in a planar configuration. The ensuing vibrational interaction leads to two carbonyl stretching bands which are normally separated by approximately 65 cm^{-1} [201-203]. An unusual situation occurs in that the 'pseudo'-symmetric vibration occurs at higher wavenumbers than the 'pseudo'-antisymmetric mode. This assignment is

confirmed by the Raman effect since it is the band at higher wave number which is polarized, and the lower, depolarized. In open-chain anhydrides the symmetric band is slightly more intense, whereas in cyclic anhydrides an intensity reversal occurs. It is even possible to distinguish between five- and six-membered ring-systems as the intensity of the higher wave-number band in the former is reduced to a relative weak absorption compared to the strong antisymmetric band[201]. The Raman data are again complementary as it is the higher wave-number band which is much more intense.

The early Raman data have been extensively reviewed by Kohlrausch[204] and laser Raman data by Dollish and coworkers[205,206]. Several studies of anhydride systems have been directed at the effect of ring-size on the carbonyl stretching wavenumbers. Strain-free six-membered ring anhydrides have almost the same band wavenumbers as aliphatic anhydrides. It is, however, in the intensities of the two bands that the effects are marked. The intensity of the low wavenumber band remains almost the same as in the aliphatic materials, whereas that of the high wavenumber band decreases dramatically. Substitution into the five-membered ring of succinic anhydride produces little marked effect[206].

In anhydrides of unsaturated 1,2-dicarboxylic acids the effect is not particularly marked, the band wavenumbers closely approximating those of aliphatic anhydrides[206]. The band wavenumbers in 2-aryl-3-methoxylmaleic anhydrides do not differ markedly from the established pattern[207]. The anhydrides of α-halogenated acids exhibit shifts of both bands to higher wavenumbers, trifluoroacetic acid anhydride absorbing at 1884 and 1818 cm^{-1} [201].

Acetic anhydride and its deuterated analogue, $(CD_3CO)_2O$, have been comprehensively examined in the gaseous, liquid and solid states by infrared and Raman methods[208].

A method of estimating glutaric and succinic anhydrides in the respective monoesters has been developed, based on the linear dependence of the absorbance of the anhydride carbonyl (at the absorption band maximum) on the anhydride content of the monoester[209]. The bands employed are at 1859 cm^{-1} in succinic anhydride and 1806 cm^{-1} in glutaric anhydride in dioxane solution.

C. Nuclear Magnetic Resonance Spectra

The availability of a proton resonance which is relatively isolated is an important requirement for quantitative analysis using p.m.r. A particular instance is provided by mixtures of aliphatic carboxylic acids and anhydrides where quantitation is particularly simple, especially in those cases where only singlet absorption bands are involved. The estimation is based on the hydrogen atoms α to the carboxyl or anhydride group. The greater rigidity of the cyclic anhydride compared to the linear anhydride increases the degree of downfield shift of the protons α to the anhydride group relative to those in the carboxyl function. The method is claimed to have been successfully applied to the analysis of maleic acid, fumaric acid and maleic anhydride[210].

D. Ultraviolet and Visible Spectra

The $n \rightarrow \pi^*$ transition in acetic anhydride occurs at 225 nm (solution in iso-octane)[92]. The spectra of four 2-aryl-3-methoxymaleic anhydrides, recorded as solutions in ethanol, have been reported[207]. 2-phenyl-3-methoxy- has absorptions at 227 and 335 nm, 2-(4-methoxyphenyl)-3-methoxy- at 239.5 and 368 nm,

2-(3-methoxyphenyl)-3-methoxy- at 234 (inflection), 263 and 333 nm and 2-(3,4-dimethoxyphenyl)-3-methoxy-maleic anhydride at 243.5, 270 (inflection), 329 (inflection) and 382 nm.

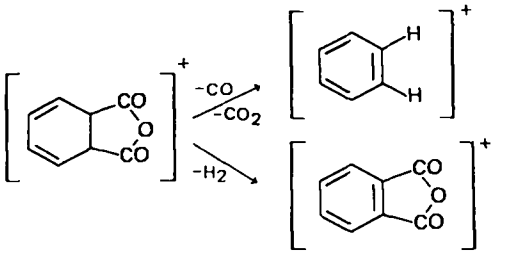
E. Mass Spectra

The mass spectra of simple aliphatic carboxylic acid anhydrides are comparatively simple, glutaric and succinic anhydrides being characterized by an absence of molecular peaks and abundant $M-CO_2$ fragments[211].

The mass spectrum of phthalic anhydride[212] possesses an intense peak at *m/e* 76 resulting from loss of carbon dioxide followed by elimination of carbon monoxide yielding the ion $[C_6H_4]^{+\cdot}$ which subsequently fragments by elimination of acetylene to produce a fragment of *m/e* 50 $[C_4H_2]^{+\cdot}$. Tetrachlorophthalic anhydride behaves in like manner except for the absence of the fragment of *m/e* 50 observed in the spectrum of phthalic anhydride. Additionally chlorine is eliminated by $[C_6Cl_4]^{+\cdot}$ and there are peaks corresponding to the doubly charged ions $[C_6Cl_4]^{2+}$, $[C_6Cl_3]^{2+}$, $[C_6Cl_2]^{2+}$ and $[C_6Cl]^{2+}$. Tetrabromophthalic anhydride also eliminates carbon dioxide, carbon monoxide and bromine, the mass spectrum containing peaks associated with the doubly charged $[C_7BrO]^{2+}$, $[C_6Br_4]^{2+}$, $[C_6Br_3]^{2+}$, $[C_6Br_2]^{2+}$ and $[C_6Br]^{2+}$ ions.

1,2,5,6-tetrahydrophthalic anhydride and hexahydrophthalic anhydride do not possess molecular ion peaks and only the former loses carbon monoxide[213]. The bridged tetrahydrophthalic anhydrides on the other hand do yield molecular ion peaks. A methylene bridge group cannot be expelled as a stable neutral fragment and the base peak is due to ionized cyclopentadiene, *m/e* 66. Alternatively when the bridge group is carbonyl the decomposition is specifically by loss of carbon monoxide and combined loss of carbon monoxide and C_2O_3[214].

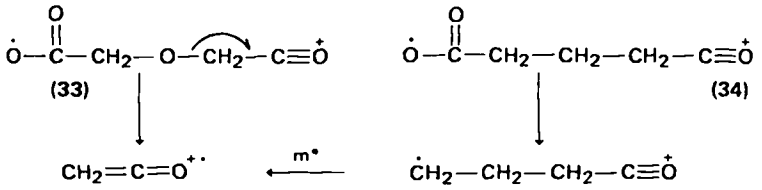
1,2-dihydrophthalic anhydride yields strong molecular ion peaks and undergoes reactions leading to aromatization of the six-membered ring by elimination of a molecule of hydrogen and of C_2O_3 (equation 19).



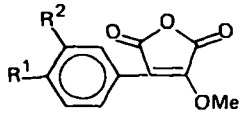
(19)

Pyridine-2,3-dicarboxylic acid anhydride fragments in a manner analogous to that observed in phthalic anhydride[212]. The resulting fragment of *m/e* 77 subsequently eliminates hydrogen cyanide.

In the mass spectra of glutaric anhydride and diglycollic anhydride the base peak is found at *m/e* 42 while the molecular ion is absent[215]. The molecular ions of both compounds undergo initial fission of the CO–O bond to yield the ions **33** and **34**. Glutaric anhydride initially loses a molecule of carbon dioxide from **34** to form the $[\dot{C}H_2CH_2CH_2CO]^+$ ion which exhibits a moderately intense peak at *m/e* 70. The mass spectrum of diglycollic anhydride, however, shows an absence of a peak at *m/e* 72 corresponding to $[\dot{C}H_2OCH_2CO]^+$ which suggests that the molecular ion fragments directly to the $[CH_2CO]^+$ ion without loss of carbon dioxide.



The mass spectra of the 2-aryl-3-methoxymaleic anhydrides **35**–**38** are relatively simple exhibiting only four or five major fragment ions[207].



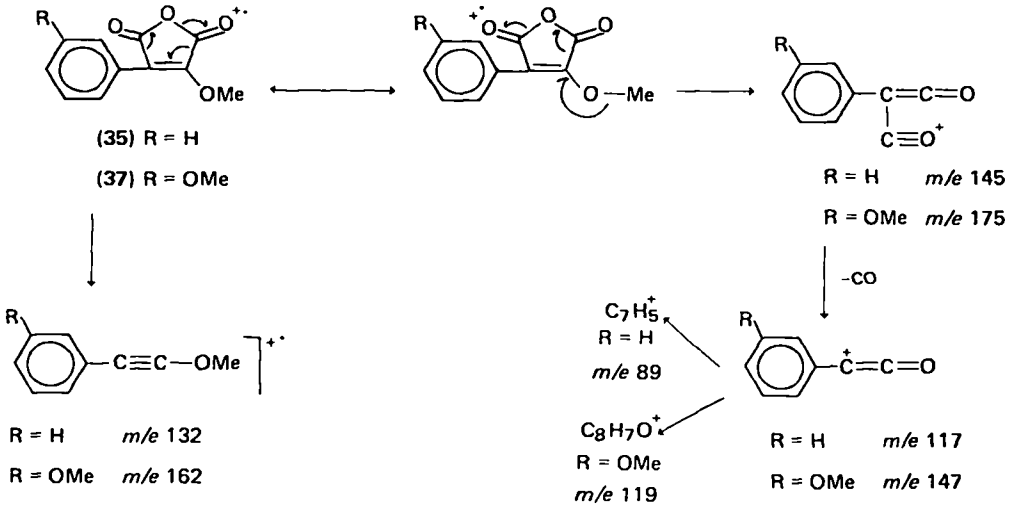
(35) $R^1 = R^2 = H$

(36) $R^1 = OMe$, $R^2 = H$

(37) $R^1 = H$, $R^2 = OMe$

(38) $R^1 = R^2 = OMe$

The spectra of **35** and **37** [2-(3-methoxyphenyl)-3-methoxymaleic anhydride] may be considered in terms of two possible modes of fragmentation which arise by initial electron abstraction from each of the carbonyl oxygen atoms.



(35) R = H

(37) R = OMe

R = H *m/e* 145

R = OMe *m/e* 175

R = H *m/e* 132

R = OMe *m/e* 162

R = H *m/e* 89

R = OMe *m/e* 119

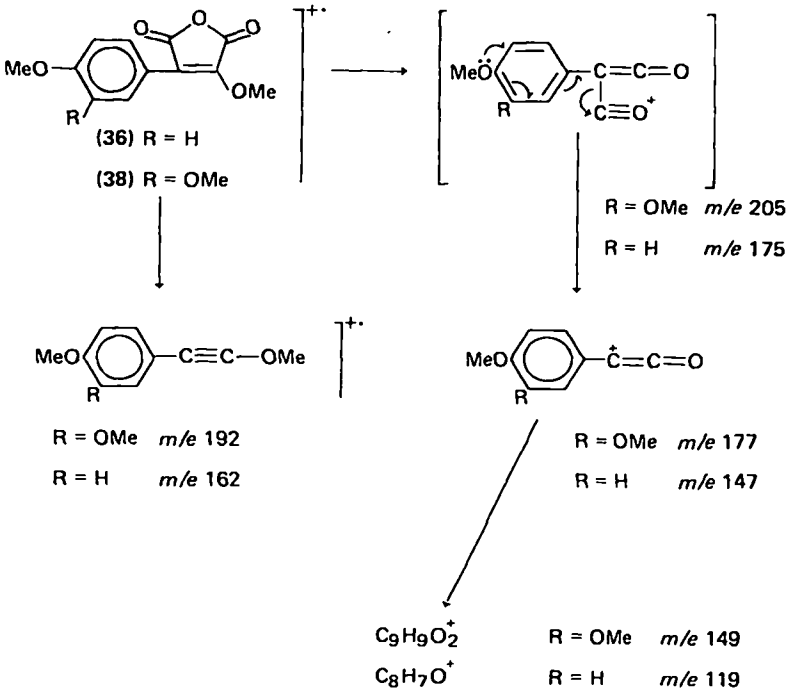
R = H *m/e* 117

R = OMe *m/e* 147

A different fragmentation pattern exists for the 4-methoxy- and 3,4-dimethoxyphenyl derivatives **36** and **38**. The presence of an intense ion at *m/e* 147 may be explained by assuming that the planarity of the hypothetical ion at *m/e* 175 and the availability of electrons from the 4-methoxy group facilitate fragmentation by loss of carbon monoxide.

F. Chromatography

Carboxylic acid anhydrides generally pose difficulties in chromatographic analyses because of their natural tendency to be partially hydrated to the corresponding acids. A gas-chromatographic technique has been employed for the quantitative analysis of maleic and citraconic anhydrides based on the observation that the methyl esters derived from maleic and citraconic acids correctly yield the amounts of anhydrides and acids initially present in a sample[216].



G. Polarographic and Titration Methods

Phthalic anhydride in an acetone–water medium may be polarographically reduced as the unhydrolysed molecule[217]. Acetone, when acidified with a small volume of dilute hydrochloric acid so as to be 0.1–0.2 mol dm^{-3} in hydrochloric acid, provides a medium in which the polarographic wave develops between −0.9 and −1.2 V, readings being taken against a standard calomel electrode. In media which are nearly neutral one or two waves may develop depending on the water content of the mixed solvent. As phthalic, benzoic and acetic acids and the anhydrides of the latter two do not produce interfering waves, phthalic anhydride may be determined in their presence.

The phthalic anhydride content of dialkyl phthalates may be determined titrimetrically using glass and calomel electrodes[218]. Phthalic anhydride and monoalkyl phthalates may be estimated by successive neutralization of the sample with 0.5 mol dm^{-3} sodium hydroxide, acidification with 0.1 mol dm^{-3} hydrochloric acid in methanol and titration with 0.1 mol dm^{-3} potassium hydroxide in mixed ethanol and methanol solvent using the electrodes mentioned previously.

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Supplement B The Chemistry of Acid Derivatives
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CHAPTER 11

The photochemistry of organic acids, esters, anhydrides, lactones and imides

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I. INTRODUCTION

A. Scope

The photoreactions of the functional groups comprised from the general formula RCX, where X is OH, OR, OCR and NHCR, have been studied for a wide variety of R groups. For the most part, these individual studies have each been focused on a relatively small number of compounds producing an extensive and very diverse body of literature on the photochemistry of acids, esters and anhydrides, in particular.

In order to limit this review to a manageable body of knowledge, the chapter will be confined to the photochemistry of organic acids, esters, anhydrides, lactones and imides and will centre attention on the photofragmentations and photorearrangements that have been observed. A notable exclusion will be the photochemistry of inorganic complexes which have been included in two recent monographs[1,2] and several reviews[3]. An additional limitation imposed is the requirement that the functional group, C–X, e.g. the carboxyl group of esters and lactones, be an integral part of the bond-making–bond-breaking processes occurring from the excited reactants. Therefore, substituent effects involving one of the five groups above on some other photoreaction will not be discussed. Reviews of the photochemistry of other functionalities should be consulted for this. Excellent bibliographies and reviews of the recent literature in photochemistry are available in *The Chemical Society Specialist Periodical Report on Photochemistry*, Volumes 1–8 (1968–1976)[4] and in *Advances in Photochemistry*, Volumes 1–10 (1963–1977)[5].

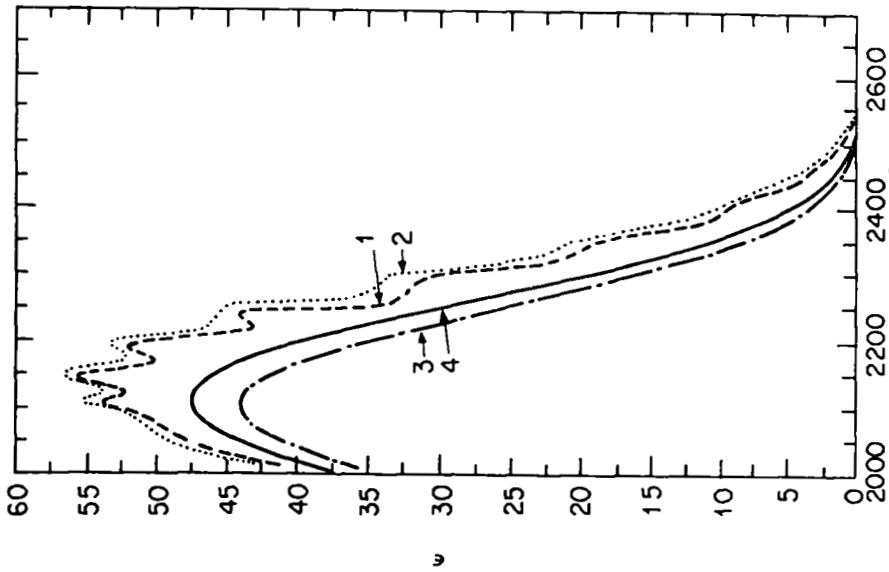
B. Organization

A comprehensive review of the literature on the photochemistry of acids, esters, anhydrides, lactones and imides necessitates additional subdivision into reaction types. Common to the photochemistry of many of these groups is fragmentation, with expulsion of carbon monoxide, carbon dioxide or other small molecules. In an attempt to systematize the currently known photoreactions of these functional groups, the order of presentation to be followed will be (*i*) reaction type, e.g. photodecarboxylation, photodecarbonylation and photoreduction. Each reaction type will then be subclassified into (*ii*) the individual functional groups to be discussed. These sections will be preceded with a brief section on general photochemical reactions in each subclass. Tables of reactions in each reaction type are provided for quick reference.

II. ELEMENTARY EXCITED-STATE PROCESSES

A. Excitation

The absorption of a photon supplies a molecule with additional energy which in most instances is sufficient to break covalent bonds. Electronic excitation of the functional groups discussed here involves excitation with ultraviolet light in the region of 280–200 nm (102–143 kcal/mol). The absorption spectra for ethyl acetate, acetic acid and acetic anhydride are typical of those for most saturated members of these classes (Figure 1). The absorption band has been assigned to an



(b) Absorption spectra for: (1) Methyl formate $[CH_3O_2CH(g)]$, 25°C. (2) Ethyl formate $[C_2H_5O_2CH(g)]$, 25°C. (3) Methyl acetate $[CH_3O_2CCH_3(g)]$, 25°C. (4) Ethyl acetate $[C_2H_5O_2CCH_3(g)]$, 25°C. From Calvert and Pitts[6].

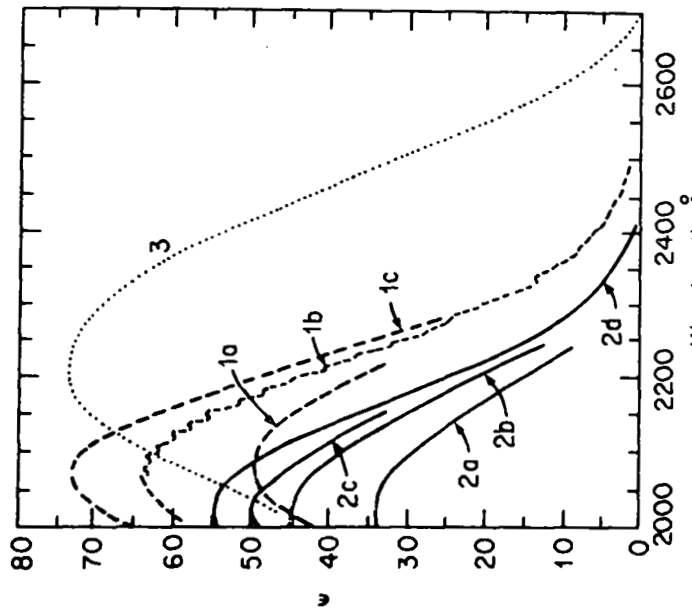


FIGURE 1. (a) Absorption spectra for: (1) Formic acid $[HCO_2H(g)]$, 27°C; (a) 2.45 mm, (b) 16.4 mm, (c) 35.2 mm; an undefined amount of monomer and dimer contribute, but calculated assuming monomer only. (2) Acetic acid $[CH_3CO_2H(g)]$, 26°C; (a) 3.6 mm, (b) 8.3 mm, (c) 11.0 mm, (d) 12.9 mm; calculated assuming monomer only. (3) Acetic anhydride $[(CH_3CO)_2O(g)]$, 25°C.

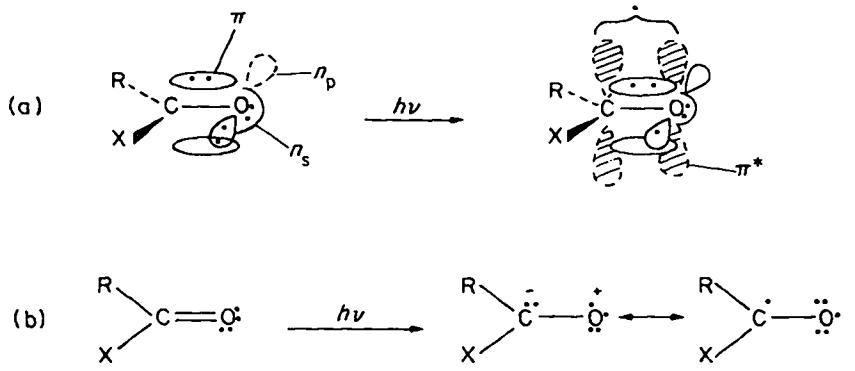
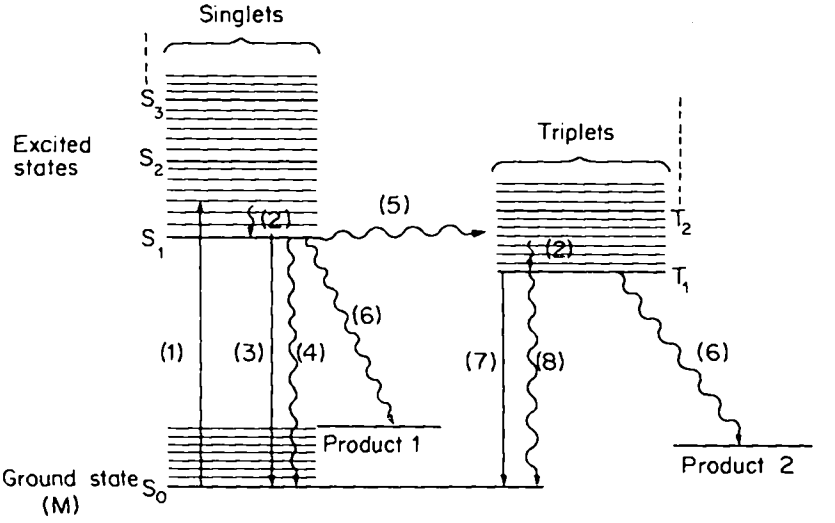


FIGURE 2. Representation of a carbonyl $n-\pi^*$ excitation.



Process		Unimolecular rate (s^{-1})	Rate constant
(1)	Absorption	10^{15}	$I_0 \epsilon [S_0]$
(2)	Internal conversion (vibrational relaxation)	10^{12}	
(3)	Fluorescence	10^6-10^9	k_f
(4)	Internal conversion	–	k_d^1
(5)	Intersystem crossing	10^7	k_{ISC}
(6)	Reaction	Variable	k_r^1, k_r^3
(7)	Phosphorescence	$10^{-2}-10^4$	k_p
(8)	Radiationless decay (from triplet)	$10^{-2}-10^4$	k_d^3

FIGURE 3. General photophysical and photochemical pathways in solution (Jablonski diagram[8]); ——→ radiative processes, ~~~~→ non-radiative processes.

$M^0 \xrightarrow{h\nu} M^1$	Absorption
$M^1 \xrightarrow{k_d^1} M^0$	Internal conversion
$M^1 \xrightarrow{k_f} M^0 + h\nu'$	Fluorescence
$M^1 \xrightarrow{k_{ISC}} M^3$	Intersystem crossing
$M^1 \xrightarrow{k_r^1}$ Product *1*	Reaction (singlet state)
$M^3 \xrightarrow{k_p} M^0 + h\nu''$	Phosphorescence
$M^3 \xrightarrow{k_d^3} M^0$	Triplet decay
$M^3 \xrightarrow{k_r^3}$ Product *2*	Reaction (triplet state)

Also:

$M^3 + Q^0 \xrightarrow{k_q} M^0 + Q^3$	Quenching

SCHEME 1. General mechanism for photoreactions.

n,π^* transition[7], i.e. promotion of a non-bonding electron to the antibonding π orbital as shown schematically in Figure 2. For comparison, the n,π^* absorption band of acetone (R = X = CH_3) is from 330 to 220 nm with a maximum located at approximately 280 nm. The hypsochromic shift of the n,π^* band for esters, acids and anhydrides is a result of the electron-donating substituent (X) adjacent to the carbonyl, increasing the n,π^* energy gap. Much of the photochemistry of the excited carbonyl can be rationalized by judicious application of these representations.

B. Excited-state Decay

The initially generated excited state has available numerous pathways with which to dissipate the excess energy. Several of these are depicted in Figure 3. Important processes for mechanistic investigations are fluorescence and phosphorescence (processes 3 and 7). Changes in reaction conditions which affect the product distributions can be independently monitored by the effect on these two emission processes. Changes in the rate of fluorescence or phosphorescence are often directly related to the changes in the rates of product formation.

As indicated in Figure 3, the lowest excited singlet (S_1) is reached quite rapidly in solution (10^{12} s^{-1}) by vibrational relaxation. Most organic molecules release the excess vibrational (and higher singlet-state) energy to the surrounding solvent cage before other processes occur. The excited singlet either reacts to form intermediates and products or undergoes one or more photophysical processes including (3) fluorescence, (4) internal conversion, or (5) intersystem crossing to the triplet state. The triplet state, in turn, may (6) react to yield the same (or different) products, (7) phosphoresce or (8) return to the ground state by a non-radiative process.

Because the events proceeding from the initially formed singlet excited state are varied and numerous, an analytical treatment of a particular reaction requires more than just the physical product yield. Two additional quantitative measures are necessary for a mechanistic analysis. The simplest of these is the quantum yield (or

efficiency) as given in equation (1). For a constant light flux, this expression can

$$\Phi_R = \frac{\text{Molecules of R formed from } S_0 \text{ per unit time}}{\text{Photons absorbed by } S_0 \text{ per unit time}} \tag{1}$$

also be written as the ratio of the rate of product formation to the rate of light absorption which in turn can be converted to the ratio of the rate for reaction to the rates for all processes occurring from the excited singlet as shown in equation (2).

Singlet product 1 *formation:*

$$\Phi_{R(1)} = \frac{d[R(1)]/dt}{dI/dt} = \frac{k_r^1}{k_f + k_d^1 + k_{ISC} + k_r^1} \tag{2}$$

Triplet product 2 *formation:*

$$\Phi_{R(2)} = \underbrace{\frac{k_{ISC}}{k_f + k_{ISC} + k_d^1 + k_r^1}}_{\Phi_{ISC}} \times \frac{k_r^3}{k_r^3 + k_p + k_d^3} \tag{3}$$

$$\Phi_{R(2)} = \Phi_{ISC} \times \frac{k_r^3}{k_r^3 + k_p + k_d^3} \tag{4}$$

C. Excited-state Reactivities

As can be seen from equations (2)–(4), the quantum efficiency is actually a ratio of first-order rate constants. Because most of the mechanistic information is determined from the effect on the rate constants of changing reaction conditions, a second requirement for thorough analysis is the determination of the rate constants for reaction (k_r^1 and k_r^3). Determination of the absolute values for the individual rate constants has been achieved only in a few instances for photochemical reactions. Instead, a number of indirect methods have been developed which yield either an approximate rate constant or more often, the relative rate constant for a systematically varied parameter. One method which has been found to give acceptable relative rates is outlined below.

The values for quantum yields are generally obtainable for most reactions (Φ_r) and for the fluorescence (Φ_f) (or phosphorescence, Φ_p) for a particular reactant. The quantum efficiencies for these processes are given by equations (2) and (5), respectively, assuming the same general scheme depicted earlier.

$$\Phi_f = \frac{k_f}{k_f + k_d^1 + k_{ISC} + k_r^1} \tag{5}$$

$$\tau = \frac{1}{\sum_i^n k_i^1} = \frac{1}{k_f + k_d^1 + k_{ISC} + k_r^1} \tag{6}$$

(for n singlet-state processes)

The reciprocal of the denominator of equation (2) or (5) is defined as the natural lifetime of the excited singlet (equation 6), so that the rate constant for

reaction can be related to the quantum efficiencies for reaction and for fluorescence by expressions (7) and (8).

$$k_r^1 = \frac{\Phi_{R(1)}}{\tau} \quad \text{and} \quad \Phi_f = k_f \tau \tag{7}$$

Substitution for τ gives:

$$k_r^1 = \Phi_{R(1)} \times \frac{k_f}{\Phi_f} \tag{8}$$

The quantum efficiencies for product formation and fluorescence are obtainable by standard isolation and fluorometric techniques. Absolute rates for fluorescence can be determined either by single-photon counting techniques[9] or by indirect methods such as fluorescence quenching[10]. A similar treatment allows the determination of rate constants for triplet reactivity with the additional complication that the intersystem crossing efficiency must be determined independently.

D. Determination of Excited-state Multiplicities

The need for proper assignment of the excited state multiplicity for a specific reaction is apparent from the treatment given above. The methods for determination of the multiplicity of the excited state that gives rise to a specific product rely principally on triplet sensitization and quenching experiments. Figure 4 diagramatically depicts the molecular events leading to energy transfer, the process of importance for quenching and for sensitization. For triplet sensitization, the donor is a molecule which will transfer only triplet energy to the reactive acceptor and ideally is photochemically inert. The intersystem crossing efficiency is the probability for triplet state production for a particular sensitizer. This indirect entry into the triplet manifold of reacting molecules bypasses the singlet excited state. Thus, any reactions observed occur from the triplet state. Those reaction products which are observed on direct irradiation but are absent when a triplet sensitizer is

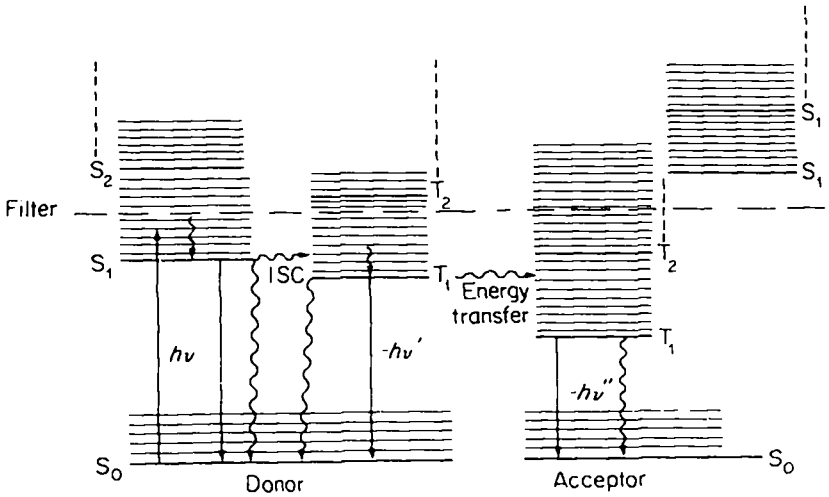


FIGURE 4. Jablonski diagram of energy transfer.

TABLE 1. Triplet sensitizers

Compound	Triplet energy[b, c] (kcal/mol)	Intersystem crossing efficiency[c] Φ_{ISC}	Phosphorescent lifetime, τ_p(s)
Benzene[a]	84	0.25	–
Acetone[a]	80.3[d]	1.00	4×10^{-4}
Propiophenone	74.8	–	3.8×10^{-4}
Acetophenone	74	1.00	4×10^{-3}
Benzophenone	68.9	1.00	5×10^{-2}
Fluorene[a]	67.6	0.31	–
Triphenylene[a]	66.6	0.85	–
Thioxanthone	65.5	1.00	–
Michler's Ketone	61.0	1.00	–
Naphthalene[a]	60.6	0.40–0.80	–
Chrysene[a]	57.2	0.81	–
Biacetyl	54.9	0.98	8×10^{-3}
Fluorenone	53.3	0.93	–
Pyrene[a]	48.2	0.1–0.4	–
Fluorescein	47.2	0.05	–
Eosin	43.0	0.71	–
Perylene[a]	36.0	0.06	–

[a] Also singlet sensitizers.
[b] G. N. Lewis and M. Kasha, *J. Amer. Chem. Soc.*, 66, 2100 (1944).
[c] P. S. Engel and B. M. Monroe, *Advances in Photochemistry*, Vol. 8, (Ed. W. A. Noyes, Jr., G. S. Hammond and J. N. Pitts, Jr.), Wiley–Interscience, New York, 1971, p. 245.
[d] R. F. Borkman and D. R. Kearns, *J. Chem. Phys.*, 44, 945 (1966). For singlet sensitization see F. S. Weltack, G. D. Renkes, M. G. Rockley, N. J. Turro and J. C. Dalton, *J. Amer. Chem. Soc.*, 92, 1793 (1970).

used are generally assigned as singlet-state products. Table 1 lists several commonly used sensitizers, their intersystem crossing efficiencies and triplet energies.

Quenching of triplet states by acceptors of lower triplet energy than the substrate provides a complementary method of analysis for reactive-state multiplicity determinations. Reactions occurring from the singlet excited state are not affected by the presence of a triplet quencher. Conversely, the reactant disappearance *and* product appearance rates are altered by the addition of a quencher for triplet-state processes. The quencher or acceptor accepts triplet energy from the

TABLE 2. Quenchers and their triplet energies

Compound	E_t(kcal/mol)
Naphthalene	61
Piperylene (1,3-pentadiene)[a]	54
Biacetyl	54.9
Oxygen[a, b]	32
Di-*t*-butyl nitroxide[a, b]	–
Ferrocene[b]	–

[a] Singlet quenchers.
[b] Paramagnetic quenchers.

reactant, here depicted as the donor (Figure 4). The process is diffusion controlled as long as the reactant triplet energy is at least 3 kcal/mol above the triplet energy of the quencher. A list of commonly used quenchers and their triplet energies is given in Table 2.

In addition to establishing the multiplicity of a product-forming excited state, quantitative analysis of the rate of quenching will provide indirect information on some of the kinetic parameters including the lifetime of the triplet excited state. For a general mechanistic scheme such as that given in Scheme 1, the quantum efficiencies without and with quencher present are given by equations (3) and (9). The ratio of the quantum efficiencies gives the standard Stern–Volmer relationship shown in equation (10), where τ^3 is the triplet lifetime of the reactant. If the energy transfer process is diffusion controlled, then $k_q = k_{dif}$

$$\Phi_{R(2),q} = \frac{k_r^3}{k_r^3 + k_p + k_d^3 + k_q[Q]} \tag{9}$$

$$\frac{\Phi_{R(2)}}{\Phi_{R(2),q}} = \frac{k_r^3 + k_p + k_d^3 + k_q[Q]}{k_r^3 + k_p + k_d^3}$$

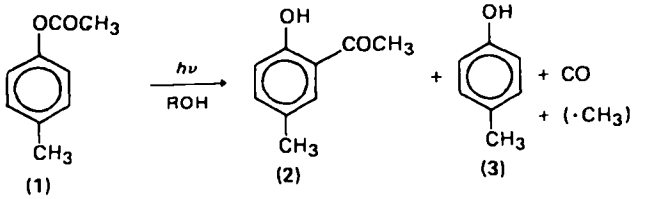
$$= 1 + \frac{k_q}{k_r^3 + k_p + k_d^3}[Q]$$

$$= 1 + k_q\tau^3[Q] \tag{10}$$

for a particular reaction solvent. This allows the determination of the substrate triplet lifetime (τ^3) from the slope of the Stern–Volmer plot, i.e. $k_q(\tau^3)$.

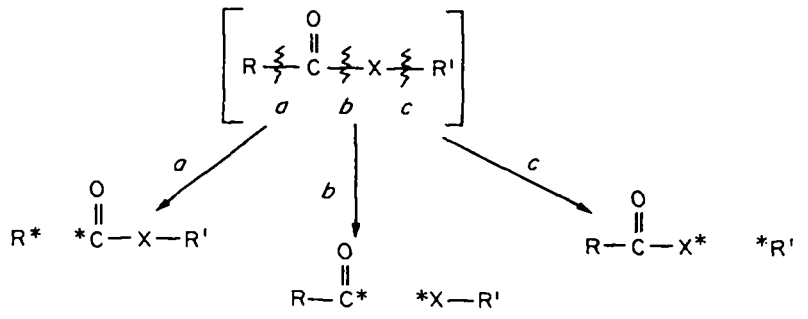
E. Excited-state Reactions

Molecules in their excited states have available numerous reactive pathways such as homolysis of sigma and pi bonds, heterolysis, ionization, bimolecular dimerization and cycloaddition, intramolecular rearrangement and many others. For the functional groups discussed in this review only a limited number of excited state reactions have been observed with any frequency. One of the most common reactions involving these groups is homolysis of the carbonyl-substituent bond, process *b* in Figure 5. This fragmentation reaction will yield a radical pair or an ion pair which subsequently reacts to form products. A typical example of this is found in the decarbonylation of aryl esters, a reaction which competes with the more familiar photo-Fries rearrangement[11]. The formation of *p*-cresol from the irradiation of *p*-tolyl acetate has been shown to occur by a homolysis of the carbonyl-oxygen bond (equation 11)[12]. The photo-Fries rearrangement product (2) may also



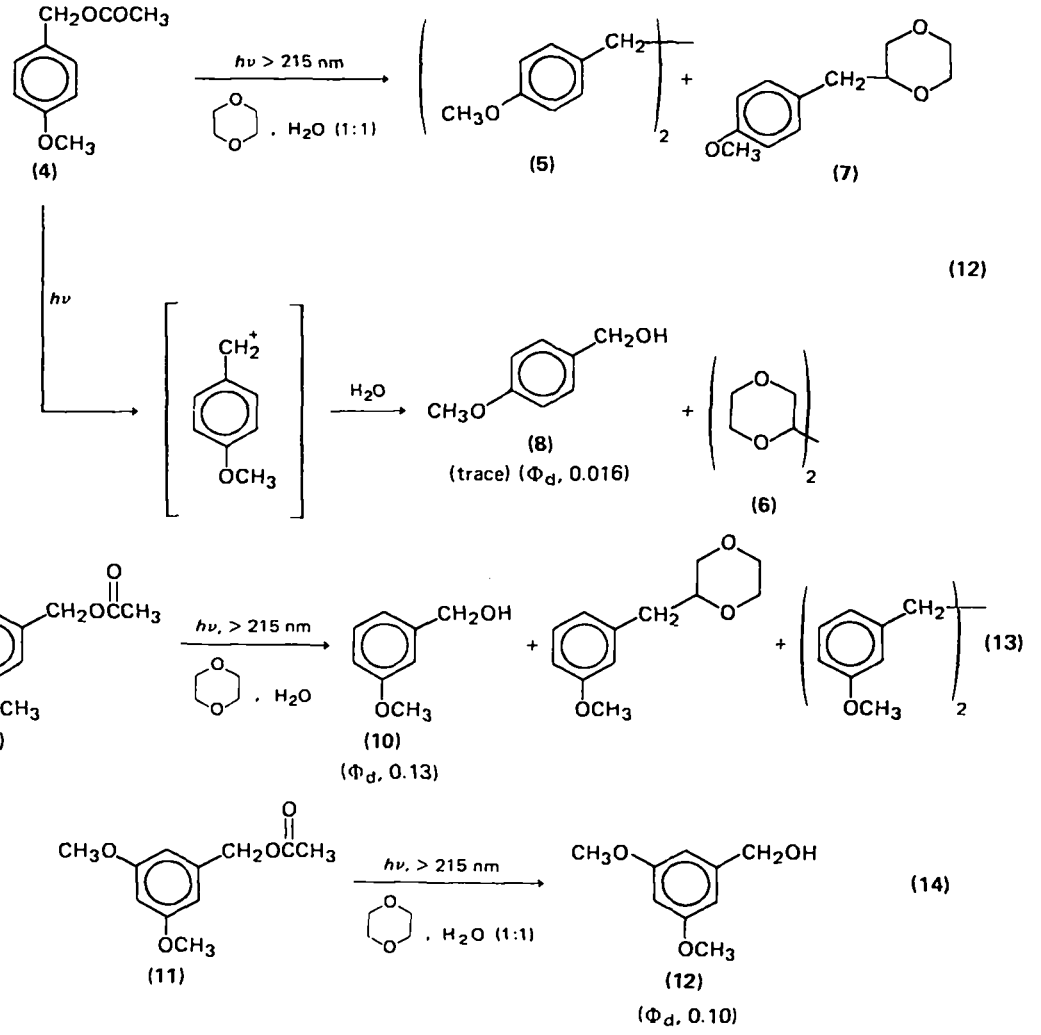
(1) (2) (3) (11)

be considered to go through a process involving an initial homolytic carbonyl-oxygen bond cleavage[13]. Recent evidence for a radical-pair intermediate in the photo-Fries rearrangement of *p*-cresol *p*-chlorobenzoate has been obtained from CIDNP studies[14].

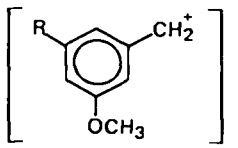


* = •, + or −

FIGURE 5. General photochemical fragmentation reactions of acids, anhydrides, esters, lactones and lactams.



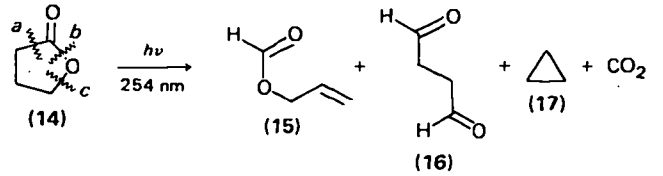
Reactions in which bond *c* has been broken have also been reported for a wide variety of functionalities. A pioneering mechanistic investigation by Zimmerman and Sandel[15] on the photosolvolysis of benzyl acetates noted *meta* activation in contrast to *para* activation in ground-state solvolysis. Irradiation of 4-methoxybenzyl acetate in dioxane–H_2O mixtures gave almost exclusively free-radical products suggestive of homolytic rupture of bond *c* (equation 12). This result was compared with the results of irradiation of the 3-methoxy- and 3,5-dimethoxybenzyl acetates (**9** and **11**) which efficiently photosolvolysed to the corresponding benzyl alcohols (equations 13 and 14). The benzyl ethers were formed when ethanol was the solvent, evidence for the benzyl carbonium ion **13** as an intermediate from heterolysis of bond *c* (however, see Section VI.B for an alternative interpretation).



(13)

R = H, OCH_3

Finally, examples of bond *a* cleavage are known. The extensive studies by Simonaitis and Pitts[16–18] on γ-butyrolactones have illustrated all three bond-rupture processes. Photolysis of γ-butyrolactone (**14**) gave four products: allyl formate (**15**), succinaldehyde (**16**), cyclopropane (**17**) and CO_2 (equation 15). Pitts



(14) (15) (16) (17) (15)

has suggested that homolytic cleavage at bond *a* generates a 1,5-diradical which disproportionates to **15** or decarboxylates and couples to yield **17** and CO_2. These latter two products may find an alternative channel through cleavage at bond *c*. The dialdehyde arises from the disproportionation of the 1,5-diradical generated by homolytic cleavage at bond *b*.

Many of the fragmentation reactions discussed can be ordered according to the bond-cleavage approach given in Figure 5, though for most studies there is little evidence for these intermediates. As in the decarboxylation step with γ-butyrolactone, the sequence of the bond-cleavage steps is even less well understood. However, the approach does provide a systematic and useful method for discussing the photochemistry of this class of compounds. Other, more fundamental, approaches to the understanding of the photochemical transformations will be discussed with each reaction type.

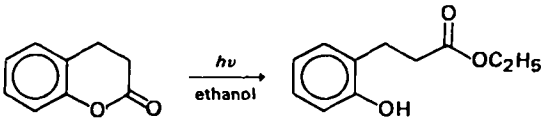
III. PHOTODECARBONYLATION

Although decarbonylation is often an efficient pathway for ketones and aldehydes[19], the carbon and hydrogen derivatives of RCOX, this process is less frequently observed for esters, lactones and lactams. Loss of carbon monoxide is a general process only for the anhydride group within these carbonyl functions. Even here, however, there is evidence that the decarbonylation occurs subsequent to an

initial photodecarboxylation of the anhydride (*vide infra*). Thus, examples of the decarbonylation process are not plentiful.

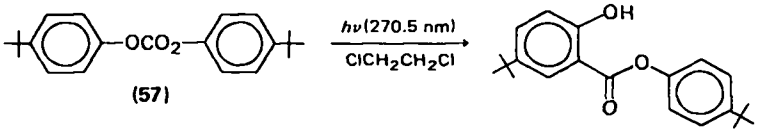
A. Esters and Lactones

Within this class of carbonyl derivatives, the decarbonylation process is most often encountered as a side-reaction of the photo-Fries rearrangement[11,20] and its analogues. The product of the decarbonylation reaction for aryl esters is the corresponding phenol and the remaining fragment abstracts hydrogen to give a hydrocarbon product. Table 3 gives a representative list of reactions which involve photodecarbonylation of esters and lactones. The first 24 esters are the acyclic naphthyl or phenyl esters and are thus candidates for photo-Fries rearrangements. In most cases, however, the photo-Fries rearrangement is accompanied by the decarbonylation reaction leading to the unsubstituted phenol. Although the presence of carbon monoxide is rarely confirmed, most authors have assumed that it is the product resulting from the decomposition of the acyl radical intermediate. In very early studies of the photo-Fries rearrangement, Anderson and Reese[23,25] suggested that the deacylated phenol resulted from a photosolvolysis reaction. Evidence in favour of this pathway was found in the irradiation of dihydrocoumarin (55) in ethanol which gave ethyl *o*-hydroxyphenylpropionate (56) as the only product (equation 16).

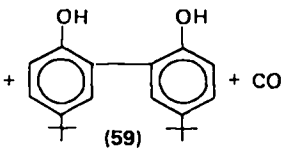


(55) (56) (16)

Subsequently, several authors have suggested that the 'lost' fragment results from a decarbonylation of initially formed acyl radicals. Barton, and coworkers[21,22] established the presence of carbon monoxide (93%) among the photoproducts of 2-naphthyl fluorene-9-carboxylate (22) and suggested that decarbonylation becomes more important as the substituents on the acid portion become increasingly radical stabilizing, e.g. R = CCl_3 to R = 9-fluorenyl. In addition to the radical stabilization parameter, the reaction requires aryl esters as reactants, an indication that light absorption or energy localization in the phenolic group is required.



(57) (58) (Φ~0.08) (17)



(59)

In an effort to establish the intermediacy of aryloxy radicals, Humphrey and Roller[33] examined the photoreactions of bisphenol-A and related diaryl carbonate

TABLE 3. Decarbonylation of esters and lactones

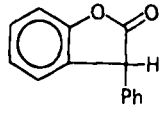
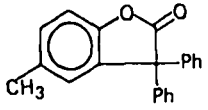
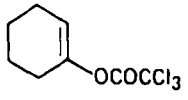
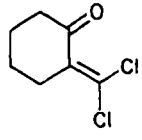
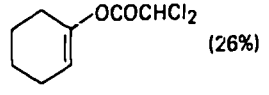
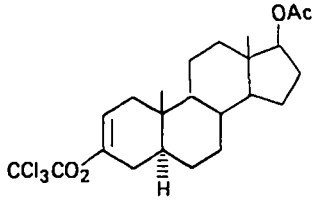
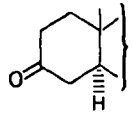
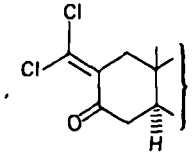
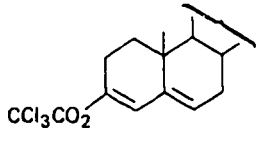
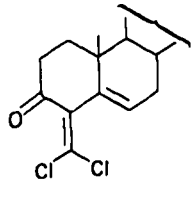
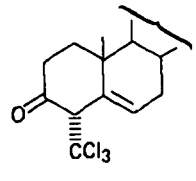
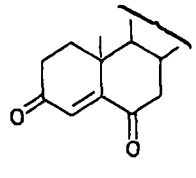
	Ester	Conditions[a]	Products (Yields)	Reference
(18)	2-Naphthyl benzoate	Hg, hp, quartz, ether	2-Naphthol (4%)	21
(19)	2-Naphthyl acetate	Hg, hp, quartz, ether	2-Naphthol (32%)	21
(20)	2-Naphthyl trichoroacetate	Hg, hp, quartz, ether	2-Naphthol (22%)	21
(21)	2-Naphthyl triphenylacetate	Hg, hp, quartz, ether	2-Naphthol (39%)	21
(22)	2-Naphthyl fluorene-9-carboxylate	Hg, hp, Pyrex, ether	2-Naphthol (60%), CO (93%)[b]	21
(23)	2-Naphthyl xanthene-9-carboxylate	Hg, hp, quartz, ether	2-Naphthol (60%)	22
(24)	2-Naphthyl *o*-thiophenylbenzoate	Hg, hp, quartz, ether	2-Naphthol (10%)	22
(25)	2-Naphthyl *o*-iodobenzoate	Hg, hp, quartz, ether	2-Naphthol (14%)	22
(26)	*p*-Cresyl fluorene-9-carboxylate	Hg, hp, quartz, ether	*p*-Cresol (58%)	21
(27)	Guaiacyl fluorene-9-carboxylate	Hg, hp, quartz, ether	Guaiacol (58%)	22
(28)	Catechol monoacetate	Hg, mp, quartz, ethanol	Catechol (46%), 2,3-dihydroxyacetophenone (22%), 3,4-dihydroxyacetophenone (18%)	23
(29)	Phenyl formate	Hg, mp, quartz, ethanol	Phenol (49%)	24
(30)	Phenyl acetate	Hg, mp, quartz, ethanol	Phenol (28%), *p*-hydroxyacetophenone (15%), *o*-hydroxyacetophenone (19%)	25, 34
(31)	Phenyl benzoate	Hg, mp, quartz, ethanol	Phenol (14%), *p*-hydroxyacetophenone (28%), *o*-hydroxyacetophenone (20%)	25, 34
(32)	*p*-*t*-Butylphenyl formate	Hg, mp, quartz, ethanol	*p*-*t*-Butylphenol (80%)	24
(33)	*p*-*t*-Butylphenyl acetate	Hg, mp, quartz, ethanol	*p*-*t*-Butylphenol (34%), 2-hydroxy-5-*t*-butylacetophenone (34%)	24
(34)	3,5-Di-*t*-butylphenyl acetate	Hg, mp, quartz, benzene	3,5-Di-*t*-butylphenol (88%)	26
(35)	3,5-Di-*t*-butylphenyl benzoate	Hg, mp, quartz, benzene	3,5-Di-*t*-butylphenol (42%) + others	26
(36)	3,5-Di-*t*-butylphenyl *p*-methoxybenzoate	Hg, mp, quartz, benzene	3,5-Di-*t*-butylphenol (36%) + others	26
(37)	Mesityl benzoate	Hg, mp, quartz, benzene	Mesitol (15%), phenylmesitylene (17%)	26
(38)	Phenyl oxalate	Hg, mp, quartz, ethanol	Phenol (25%)	24
(39)	*p*-*t*-Butylphenyl oxalate	Hg, mp, quartz, ethanol	*p*-*t*-Butylphenol (46%)	24
(40)	 3-Phenylisocoumaranone	Hg, lp, 245 nm, methanol	*o*-Hydroxybenzhydrylmethyl ether (30%), xanthene (3%), *o*-benzylphenol (11%), *o*-hydroxybenzophenone (14%), 3-phenyl-3-hydroxyisocoumaranone (5%)	27

TABLE 3. (Continued)

Ester	Conditions[a]	Products (Yields)	Reference
(41) 	Hg. mp, Corex, methanol	2-Hydroxy-4-methyltriphenyl-methane (?)	27
(42) $CH_3CH{=}CCH_2CH_3$ $\vert$ $OCOCCl_3$	Hg, 1p, quartz 254 nm, *t*-butyl alcohol	$CH_3CH_2COCH(CCl_3)CH_3$ (12%)	28
(43) 	Hg, 1p, quartz 254 nm, *t*-butyl alcohol	 (6%),  (26%)	28
(44) 	Hg, 1p, quartz 254 nm, *t*-butyl alcohol	 (7%),  (7%), dimers	28
(45) 	Hg, 1p, quartz 254 nm, *t*-butyl alcohol	 (6%),  (9%),  (21%)	28

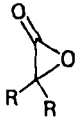
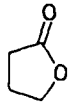
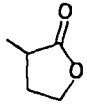
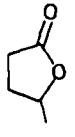
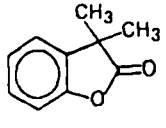
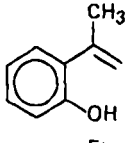
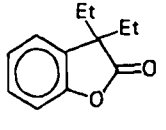
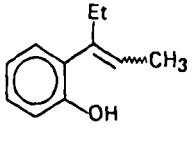
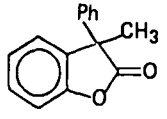
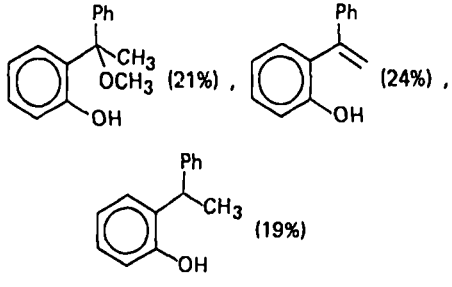
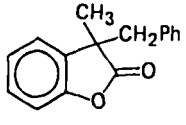
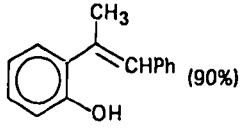
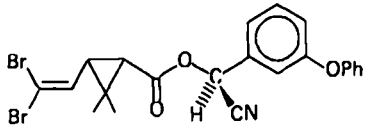
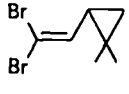
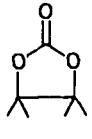
(46)	 (R = CH_3, n-C_4H_9, $(CH_2)_4$, $(CH_2)_3$)	Hg, quartz, 77 K, neat	CO, R_2CO, polymer	29
(14)		Hg, mp, monochromator 254 nm, quartz neat	Allyl formate (Φ, 0.23), succinaldehyde (Φ, 0.06), cyclopropane (Φ, 0.013), carbon dioxide (Φ, 0.015), carbon monoxide (Φ, 0.01)	17, 18
(47)		Hg, mp, monochromator 254 nm, quartz neat	Crotyl formate (Φ, 0.39), 2-methylsuccinaldehyde (Φ, 0.05), methylcyclopropane (Φ, 0.027)	16
(48)		Hg, mp, monochromator 254 nm, quartz neat	3-But-1-enyl formate (Φ, 0.18), 4-oxopentanal (Φ, 0.01), methylcyclopropane (Φ, 0.004), ethylene (Φ, 0.005)	16
(49)		Hg, quartz, pentane		30
(50)		Hg, 1p, 254 nm, quartz, pentane		30

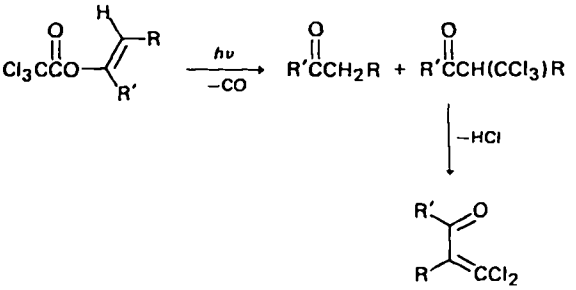
TABLE 3. (Continued)

Ester	Conditions[a]	Products (Yields)	Reference
(51) 	Hg, 1p, 254 nm, quartz, methanol		30
(52) 	Hg, 1p, 254 nm, quartz, hexane	 (90%)	30
(53) 	Hg, mp, Pyrex, methanol	 (4%), $ArCO_2CH_3$ (24%), ArCHO (8%) and others	31
(54) 	Hg, 1p, vapour phase	$(CH_3)_2CO$, CH_2CHCH_3, C_2H_4, C_2H_2	32

[a]The conditions when reported are listed in the following order: type of lamp, lamp pressure (lp = low, mp = medium and hp = high), wavelength region or filter used and solvent.
[b]By titration with I_2O_5.

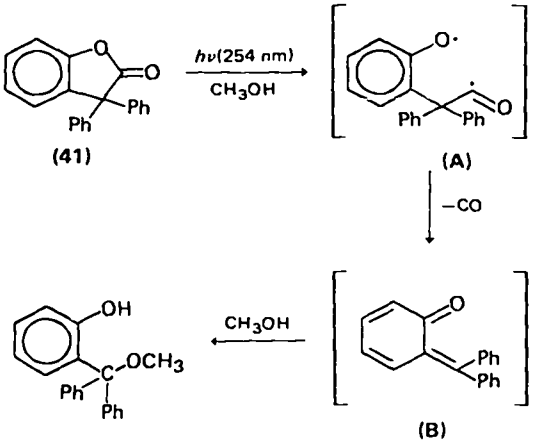
esters by flash techniques. Evidence for aryloxy radicals was obtained by flash experiments with **57** (equation 17) and with *p-t*-butylphenol (**60**). Absorption spectra at 5 μs after the flash of **57** were nearly identical with those obtained from **60**. Similar spectra were obtained from other acyclic esters. For the cyclic carbonates of bisphenol-A, no transients were observed. The authors have suggested that a concerted migration to the photo-Fries product obtains here.

Enol acetates undergo a 1,3-acyl migration analogous to the photo-Fries rearrangement[11,20] and also give decarbonylated products. Again, this is an important process for those esters which yield stable decarbonylated radical pairs. Libman, Sprecker and Mazur[28] found that enol and dienol trichloroacetates invariably gave considerable yields of decarbonylated products (equation 18). In fact, unlike the corresponding enol acetate analogues[33,34], no acyl migration products are found in the trichloroacetate series. Thus homolytic cleavage of the ether-oxygen carbonyl-carbon bond generates a radical pair which decarbonylates very rapidly. Since no products from cross-coupling were observed, solvent cage effects must be important.

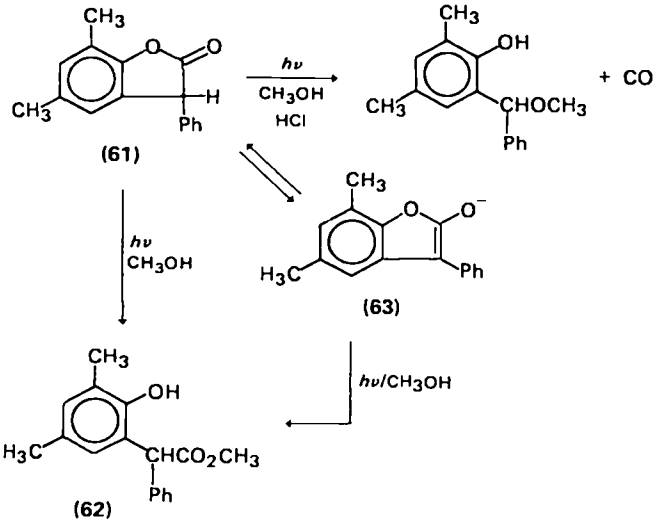


(18)

For lactones, decarbonylation is again the important process if the diradical initially generated can decarbonylate to a new, stable species (either a new diradical or a stable intermediate). Diphenylbenzofuran-2-one (**41**)[27], for example, yields *o*-quinone methide (**B**), an intermediate suggested by Gutsche[30] for several other benzofuran-2-ones (equation 19). No evidence is available for the intermediacy of diradical **A** which apparently undergoes decarboxylation faster than hydrogen abstraction from solvent or intramolecular recombination to give the phenol expected from a photo-Fries rearrangement. Padwa and coworkers[27] have also shown

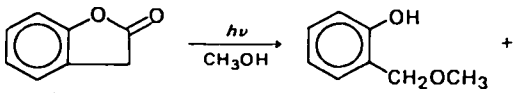


(19)



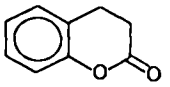
(20)

that the keto–enol tautomeric forms control the photochemistry of the benzofuranones. For example, **61** undergoes photodecarbonylation most efficiently in slightly acidic methanol, whereas in neutral methanol **61** gave only photohydrolysis products (**62** and its photoproducts) (equation 20). Control experiments and analysis of absorption spectra established that enolate **63** was the photoreactive intermediate leading to **62**. Formation of the corresponding enolates was also suggested for other furanones in the series. The absence of enolate for the parent furanone (**64**) (equation 21) was advanced as reason for its higher decarbonylation efficiency [$\Phi = 0.20$ (**64**) vs 0.058 (**61**)]. The observed wavelength dependence for certain members of this series is also explainable by the keto–enol equilibrium. Since neither sensitization by benzophenone nor quenching by piperylene was effective, the reactive excited state was assigned to the singlet[27,35].

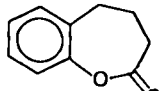


(64) (21)

Increasing the number of carbons between the aromatic ring and the lactone carbonyl causes the reaction to follow a new course. Photosolvolysis (discussed in Section VI) becomes the dominant reaction. Gutsche and Oude-Alink[36] found no

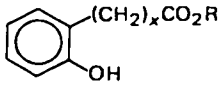


(65)

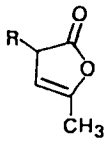


(66)

evidence for photodecarbonylation of dihydrocoumarin (**65**) or the tetrahydrobenzoxepin (**66**). Instead, alcoholic solutions of **65** or **66** were converted to their corresponding phenolic esters (**67**).

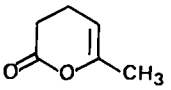


(67)



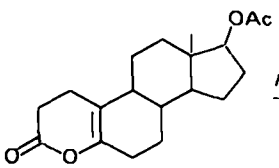
(68) R = H, CH_3

$$\xrightarrow{h\nu} \underset{(70)}{RCH{=}CHCOCH_3} + CO \qquad (22)$$



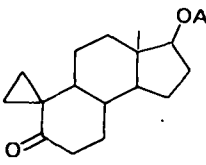
(69)

$$\xrightarrow[7\,h]{h\nu(254)} CH_2{=}C{=}O + \underset{45\%}{\text{cyclopropyl-}COCH_3} + \underset{18\%}{CH_2{=}CHCOCH_3} \qquad (23)$$



(71)

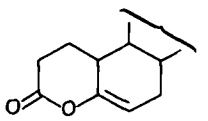
$$\xrightarrow[20\,min]{h\nu(254)}$$



(72)
40%

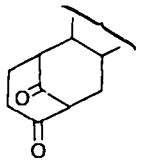
$$+ CO \qquad (24)$$

The same ring-size dependence is found in simpler enol lactones **68** and **69**. Yogev and Mazur[34] obtained 30–40% yields of methyl vinyl ketones (**70**) from **68** via decarbonylation (equation 22). However, the δ-enol lactone **69** gave photofragmentation products as well (equation 23). This photodecarbonylation reaction is not general, however. The steroidal lactone **73** undergoes a 1,3-acyl migration to a diketone upon direct irradiation (equation 25).



(73)

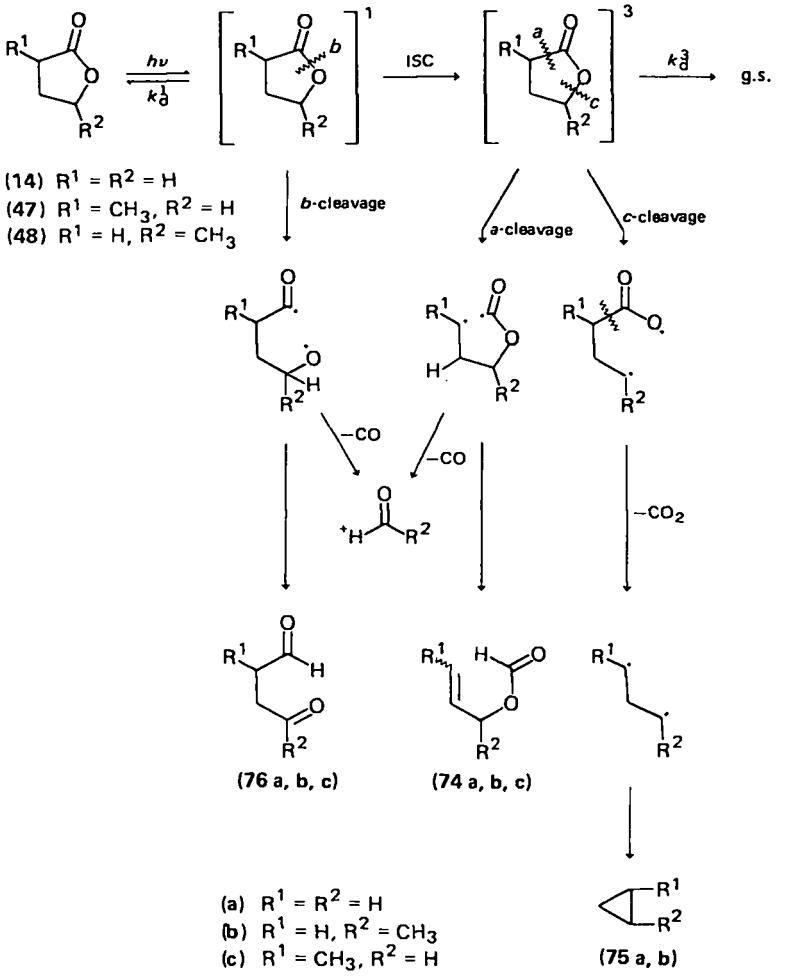
$$\xrightarrow[18\,h]{h\nu(254)}$$



$$\qquad (25)$$

Meyer and Hammond[13] have reported that decarbonylation is the probable course of reaction when phenyl *n*-butyrate or phenyl acetate is irradiated in the vapour phase. The major product from phenyl acetate was phenol(65%). The fate of the acetyl radical was not completely determined although *o*- and *p*-cresol were identified among the products. Interestingly, little *o*- or *p*-hydroxyacetophenone was found, an indication that the photo-Fries rearrangement may involve a radical-pair intermediate which later couples to form the acyl derivatives. In the gas phase, this radical pair diffuses and fails to couple[13].

Saturated lactones also undergo photodecarbonylation, although the yields are generally low and the product mixtures complex. The most comprehensive examination of this reaction is that of Simonaitis and Pitts[16] cited earlier. γ-Butyrolactone and γ-methyl-γ-butyrolactone were examined for structural and wavelength effects on the photoreactivity of 5-membered ring lactones. The products, shown in Scheme 2, illustrate the complexity of this reaction. Photodecarbonylation is a minor pathway ($\Phi_{-CO} = 0.01$ vs $\Phi_{74} = 0.23$ for **14**) and the reaction pathway is uncertain. Reasonable pathways can be envisaged through intermediates generated by cleavage of *b* (singlet-state process) or *a* (triplet-state



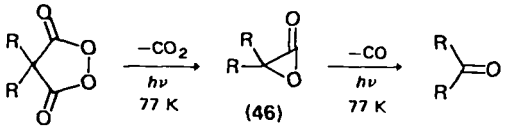
SCHEME 2.

process). The intermediacy of the two excited states (discussed in Section IV) was established by quenching experiments with 2-pentene, biacetyl and 2-butene. For unsubstituted and γ-methyl lactones **14** and **48**, efficient quenching of **74** and **75** formation was observed while **76** formation was not quenched. Interestingly, for the α-methyl derivative **47**, no quenching was observed. An examination of the triplet lifetimes of **14** and **48** ($\tau_{14} = 1.2 \times 10^{-9}$ s and $\tau_{48} = 0.7 \times 10^{-9}$ s) suggests that the methyl group in the α-position enhances the reactivity of **47**, thus reducing its lifetime below a level necessary for diffusion-controlled quenching. Unfortunately, the effect on Φ_{CO} was not reported, precluding an analysis of the excited-state precursor to decarbonylation.

The wavelength effect, determined by irradiation at 253.7 and 238.0 nm, was pronounced for the formation of **76** ($\Phi_{238}/\Phi_{254} = 2$), again suggesting a singlet-state precursor. The authors[16] invoke a vibrationally excited first-excited singlet

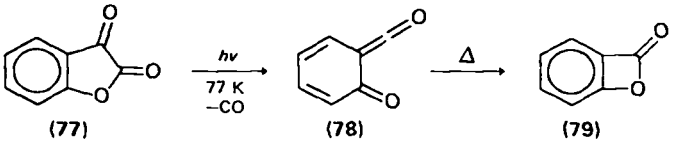
state to explain the enhanced quantum efficiency for the 238 nm irradiation. Again, information on the decarbonylation process was not reported.

Although the mechanistic details are not available on the decarbonylation reactions of esters and lactones, applications of the reaction have been reported. Chapman and coworkers[29,37] have shown that a number of α-lactones (46)



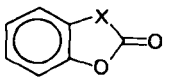
(26)

decarbonylate quite readily to ketones at 77 K; the α-lactones themselves were generated by a photodecarboxylation reaction from cyclic peroxyanhydrides[38]:



(77) (78) (79) (27)

Similarly, Michl[39] has generated keto-ketene 78 by irradiation of ketolactone 77 (equation 27). Chapman and McIntosh[40] have observed the same reaction for a number of esters and lactones of the general structure 80



(80)

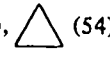
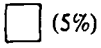
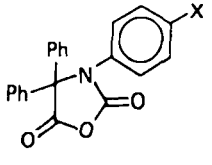
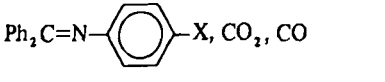
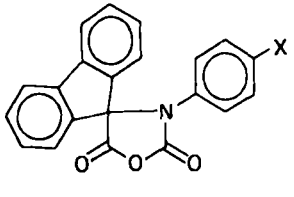
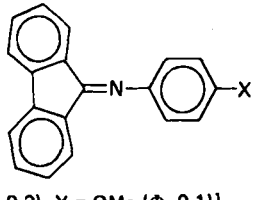
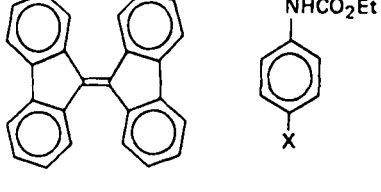
X = CH_2, O and S

B. Anhydrides

Decarbonylation coupled with decarboxylation is the major mode of photochemical reaction of anhydrides. The question of which fragment (CO or CO_2) is expelled initially or whether both are extruded simultaneously has not been answered, though an analysis of photoproducts would suggest a stepwise sequence of decarboxylation followed by decarbonylation. Early studies (1950–1955) on the gas-phase photolysis of acetic anhydride and related systems by Ausloos[41] and by Taylor[42,43] showed that the combined process was efficient, particularly at elevated temperatures (170°C). In 1969, Krull and Arnold[44] expanded the study of anhydrides to include a number of cyclic analogues. Mercury-sensitized, vapour-phase irradiation of succinic, glutaric and adipic anhydride gave ethylene and acetylene, and, for the latter two, cyclopropane and cyclobutane, respectively. These studies opened the way for more detailed and structurally varied investigations. Table 4 provides a representative list of anhydride photodecarbonylation and decarboxylation reactions.

Among these studies, two are singled out. The first is a group of studies which have established the radical intermediates for these reactions[45,46]. The second is a comprehensive mechanistic and application study of the photodecarbonylation-decarboxylation of phthalic anhydride derivatives by Zweig, Henderson and coworkers[47–51].

TABLE 4. Photodecarbonylation of anhydrides

	Anhydride	Conditions[a]	Major products (yields)	Reference
(81a)	$(CH_3CO)_2O$	Grating monochromator, Hg, mp, quartz (1849 Å), gas phase, 30–190°C	CO, CO_2, CH_2CO, C_2H_6, CH_4	41–43
(81b)	$(CH_3CH_2CO)_2O$	Hg, mp, grating quartz (1849 Å), gas phase, 30–190°C	CO, CO_2, C_2H_4, C_2H_6, CH_3CHCO, C_4H_{10}	41
(82a)	Succinic anhydride	Hg-sensitized, gas phase	CH_2CH_2 (15%), C_2H_2 (38%)	44
(82b)	Glutaric anhydride	Hg-sensitized, gas phase	C_2H_4 (5%), C_2H_2 (23%),  (54)	44
(82c)	Adipic anhydride	Hg-sensitized, gas phase	C_2H_4 (23%), C_2H_2 (54%),  (5%)	44
(83)	*cis*-1,2-Cyclobutanedicarboxylic anhydride	Hg-sensitized, gas phase	C_2H_4 (8%), C_2H_2 (30%), butadiene (4%), cyclobutene (8%)	44
(84)	Maleic anhydride	Hg-sensitized, gas phase	C_2H_2 (83%)	44
(85)	Dimethyl maleic anhydride	Hg-sensitized, gas phase	Dimethylacetylene (33%) and others	44
(86)	Perfluoroacetic anhydride	Hg, mp, quartz, gas phase	C_2F_6, CO, CO_2	45
(87)	Perfluoropropionic anhydride	Hg, mp, quartz, gas phase	n-C_4F_{10}, CO, CO_2	46
(88)		254 nm, ethanol	 X = H (Φ, 0.4), X = NMe_2 (Φ, 0.1), X = NO_2 (Φ, 0.2)	47
(89)		254 nm, benzene	CO_2, CO,  [X = H (Φ, 0.2), X = OMe (Φ, 0.1)] 	47, 49

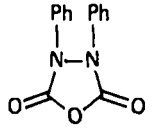
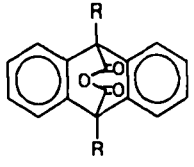
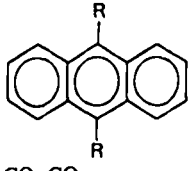
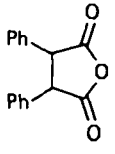
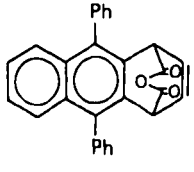
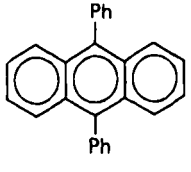
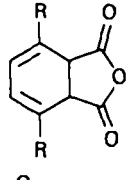
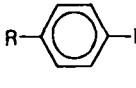
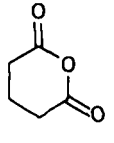
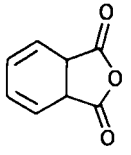
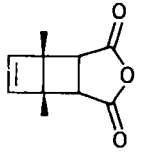
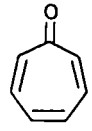
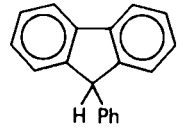
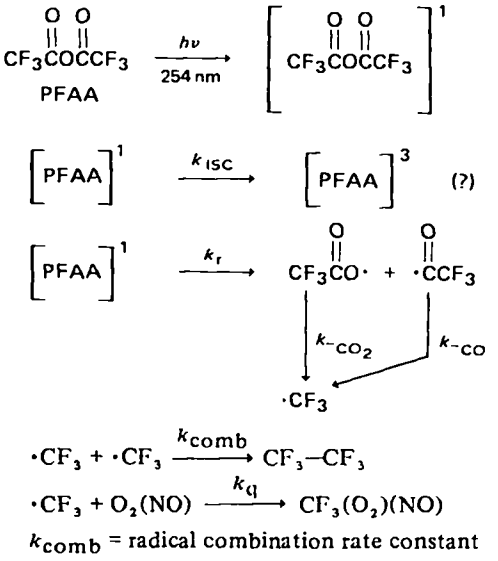
(90)		254 nm, hexane	*cis*-PhN=NPh, CO, CO_2 (Φ, 0.15)	50, 49
(91a–c)	 (a) R = H, (b) R = CH_3, (c) R = Ph	Hg, hp, Vycor, CH_2Cl_2	 [R = H (Φ, 0.42); R = CH_3 (Φ, 0.67); R = Ph (Φ, 0.46)] CO, CO_2	51, 49
(92)	 *cis* and *trans*	Hg, hp, Vycor, CH_2Cl_2	PhCH=CHPh (Φ > 0.20), CO, CO_2	49, 51, 52
(93)		Hg, hp, Vycor, CH_2Cl_2	 (Φ, 0.65), CO, CO_2	49, 51
(94a,b)		Hg, hp, Vycor, ether	 (70–80%), CO, CO_2	49, 52–54
(82)		Hg-sensitized, 254, gas phase	 (Φ, 0.48), CO (Φ, 0.56), CO_2 (Φ, 0.5),  (Φ, 0.41), $H_2C{=}CH_2$ (Φ, 0.037)	55

TABLE 4. (Continued)

Anhydride	Conditions[a]	Major products (yields)	Reference
(94a) 	Hg, 1p, 254 nm, quartz CH_3CN	 (Φ, 0.02), CO, CO_2  (Φ, 0.12),  (Φ, 0.01)	56
(95) $PhCH_2CO_2COCH_2Ph$	Hg, 1p, quartz CH_3CN	$PhCH_2CH_2Ph$, $PhCH_2COCH_2Ph$, CO, CO_2	57
(96) $Ph_3CCO_2COCPh_3$	Hg, 1p, quartz $PhH-CH_3CN$	Ph_3CH,  CO_2, CO	57

[a] See Table 3 for format.

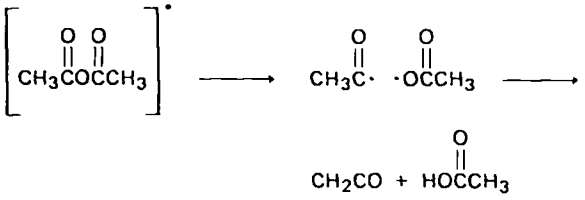
In the first of these studies, the photoextrusion of CO_2 and CO from perfluoro anhydrides[45,46] produced perfluoro alkyl radicals which were scavenged by nitrous oxide and by isobutene. The yields of CO and CO_2 were altered very little by the scavangers, however. Thus, it would appear that the initial fragmentation is either a simultaneous loss of CO and CO_2 to yield the perfluoro radicals or that the carbonyl radical intermediates are very unstable and decarbonylate (or decarboxylate) very rapidly. One such series of steps is outlined in Scheme 3.



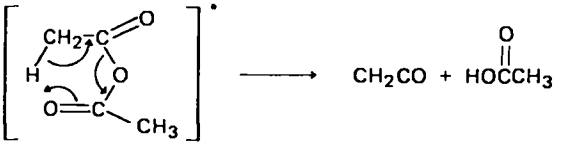
SCHEME 3. Photodecomposition of perfluoroanhydrides.

The reactive excited state was assumed to be the short-lived excited singlet state ($\tau \ll \tau_f^0 \cong 4 \times 10^{-7}$ s, calculated from the absorption spectra) from the inability of nitric oxide or 2-pentene to quench the formation of CO or CO_2. In the experiments with NO, the formation of hexafluoroethane was completely eliminated (<0.3% of the CO yield), which demonstrated the intermediacy of trifluoromethyl radicals prior to the product-forming step, thus ruling out any concerted CO and CO_2 extrusion with concommitant carbon–carbon bond formation. A modest dependence of the quantum yield on temperature was noted, increasing by a factor of 1.2 from 20 to 213°C for pentafluoropropionic anhydride.

In contrast to the uncomplicated photolysis of its perfluoro analogue, acetic anhydride undergoes two primary processes; (*i*) initial fragmentation of the C—O bond followed by decarbonylation from the acetyl radical and decarboxylation from the acetoxy radical as illustrated above and (*ii*) hydrogen migration to give



(28)

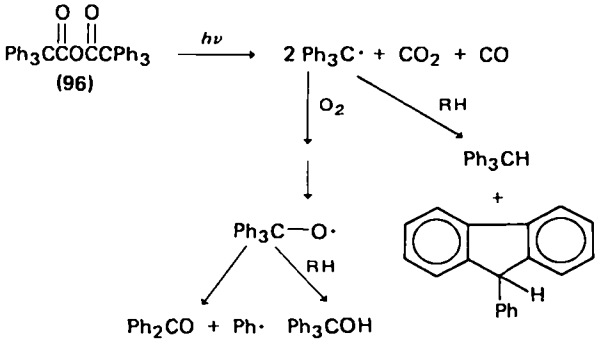


(29)

acetic acid and ketene[41]. These latter products could arise by either an initial fragmentation and disproportionation (equation 28) or a concerted decomposition step (equation 29). To date there is no firm evidence which excludes or establishes either of these possible pathways.

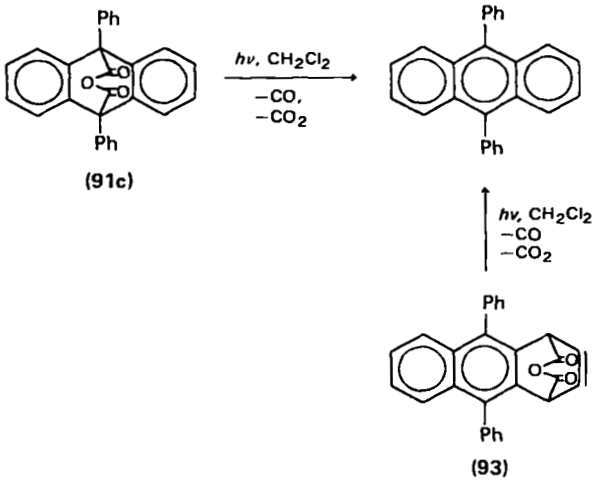
Finally, the intermediacy of aryl radicals has been demonstrated for the solution photodecarbonylation–photodecarboxylation of arylacetic anhydrides by Cerfontain and coworkers[57]. Phenylacetic and di- and triphenylacetic anhydrides were shown to lose CO_2 when irradiated at 254 nm in acetonitrile. Carbon monoxide was also expelled efficiently although a measurable yield of the ketone from the loss of carbon dioxide alone was also observed for the first two anhydrides. Hexaphenyl acetone was not formed from **96**, indicating that CO expulsion was faster than recombination.

The main photoproducts from the phenyl and diphenylacetic anhydrides were the aryl ethanes from combination of the radicals generated. Evidence that radicals were indeed involved was obtained by oxygen-trapping experiments with the triphenylacetic anhydride. The main products were triphenylmethane and fluorene in the absence of oxygen. In aerated solutions, the product composition also included triphenyl carbinol, benzophenone and biphenyl which arose from the route suggested in equation (30). Again it was noted that the efficiency of disappearance of **96** was unaffected by the presence of oxygen, implicating the excited singlet state as the reactive precursor to the initial photodecarboxylation step.

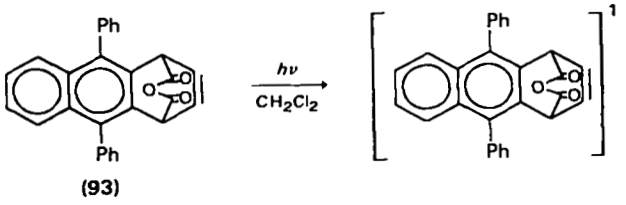


(30)

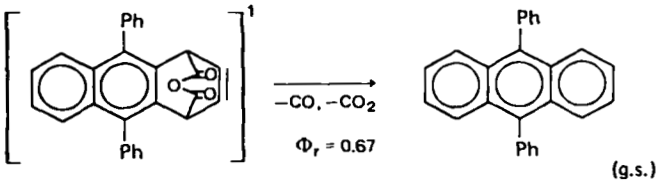
The second area where anhydride photodecarbonylation has been systematically studied has been that of bicyclic and tricyclic anhydrides which lead to potentially fluorescent products. Zweig[49,51] has examined a series of anhydrides for which the photoproduct is a known fluorescent hydrocarbon. For example, anhydride **91c** efficiently emits CO_2 and CO upon photolysis at 254 nm to produce 9,10-diphenylanthracene (equation 31). Likewise, anhydride **93** yields the same product. In neither case could the reaction be sensitized by acetone, acetophenone or benzene, implicating a singlet excited state. Of interest was the complete absence of any emission from 9,10-diphenylanthracene as it was produced in the reaction. This was taken as conclusive evidence that the photoreaction proceeded by steps (32) and



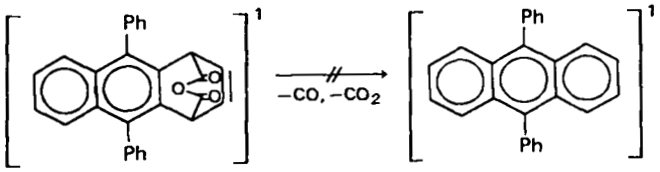
(31)



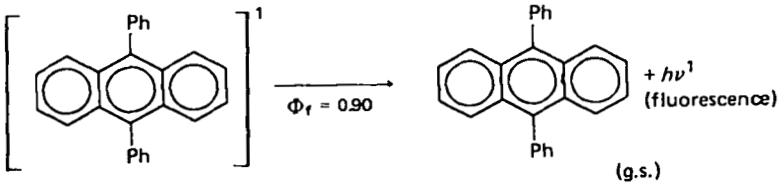
(32)



(33)



(34)

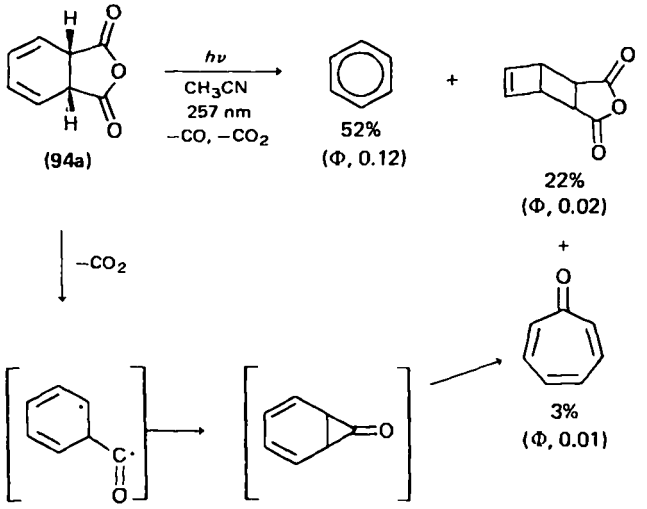


(35)

SCHEME 4.

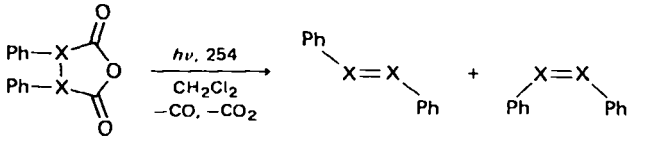
(33) in Scheme 4 and that steps (34) and (35) could not have occurred to greater than one part in ten thousand. Thus, the energy profile for this reaction can be characterized as leading directly from the excited singlet of **91c** or **93** to a ground electronic state of 9,10-diphenylanthracene and not via its excited singlet (fluorescent) state.

In addition to the bridged anhydrides, Zweig[49,51] Prinzbach[52,53] and Fuchs[56] have investigated a variety of dihydrophthalic anhydride and diphenylsuccinic anhydride derivatives. Each of these was shown to undergo efficient decarboxylation–decarbonylation to the corresponding double-bonded compound (see Table 4, **92** and **94**). In a few cases, products arising from decarboxylation alone were evident[52,56] Fuchs[56] has shown, for example, that the parent dihydrophthalic anhydride **94a** gave tropone in addition to benzene and bicyclo[2.2.0]-hexene-2,3-dicarboxylic anhydride. Tropone presumably arises from the diradical intermediate as shown in equation (36). Triplet quenchers do not affect the efficiency of disappearance of **94a**.



(36)

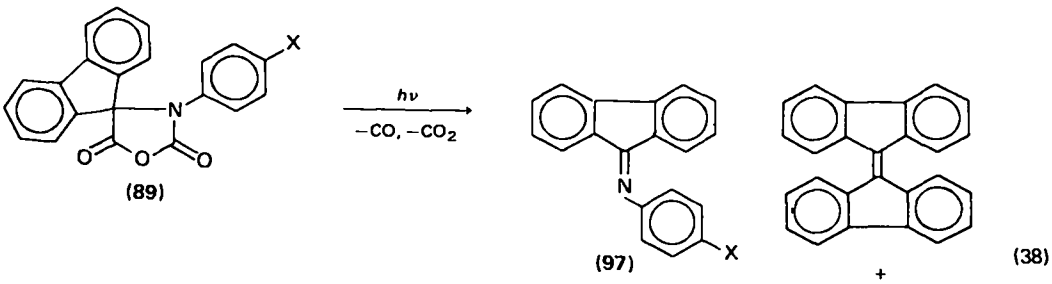
The succinic anhydrides and their aza and diaza derivatives also display high photoreactivity. Equation (37) summarizes many of the examples available from



(37)

(92) X = CH ($\Phi_d \geq 0.2$; *cis* or *trans*)[51] relative yields not determined
(90) X = N (Φ_d, 0.15)[50] 10% 90%

studies by Henderson and Zweig[47,48,50]. Again, sensitization failed and quenchers had no effect on the reaction, pointing to singlet-state reactivity[50,51]. For the azasuccinic anhydrides, the mode of fragmentation was shown to be sensitive to the



(38)

X = H	0%	100%
X = OCH_3	29%	71%
X = $N(CH_3)_2$	100%	0%
X = NO_2	very slow reaction	

substituents on the aromatic ring. Equation (38) illustrates the effect for triarylazasuccinic anhydride derivatives. These substituent effects point to a common feature in many of the photofragmentation reactions of anhydrides as well as of esters, lactones and to some extent acids; i.e. a controlling factor is the relative absorptivity of the aryl substituents. For the triarylazasuccinic anhydrides, the fluorene ring represents the lowest energy (singlet) chromophore for the unsubstituted and the *p*-methoxy derivative while the *p*-$N(CH_3)_2$ and *p*-NO_2 groups shift the absorption of the aryl groups bathochromically and these become the lowest energy chromophores (Figure 6a and b). Zweig and Henderson[47,48] have developed a sunburn dosimeter from the photoreaction of (89) [X = $N(CH_3)_2$]. The appearance and intensity of the red photoproduct 97 resulting from photodecarboxylation and decarbonylation of 89 can provide an estimate of the sun's ultraviolet intensity during a given interval.

In summary, though few other practical applications have been discovered for the photolysis of anhydrides, the examples published to date do indicate that this reaction is unusual in its high efficiency, in its general predictability and its freedom from side-reactions. Most reported examples have shown this to be a singlet reaction. Every one of the substituted anhydrides which give decarboxylation and decarbonylation are clearly substituted anhydrides where the chromophore is one atom removed from the anhydride carbonyl. Enough examples of decarboxylation without decarbonylation exist to allow a suggestion that these are stepwise reactions with decarboxylation occurring first and decarbonylation following.

C. Lactams and Imides

Only a few examples are available on the decarbonylations of these derivatives, and these cannot be construed as general. A photodecarbonylation will occur from the three-membered ring lactam analogous to the α-lactones 46 discussed in Section A. Talaty and coworkers[58] found that α-lactams derived from adamantyl and *t*-butyl derivatives fragmented in high yield to the imines (e.g. equation 39).

A correlation with the reactivity of anhydrides can be made for imides. Fuchs[56b] has shown that decarbonylation along with loss of CONH and CO

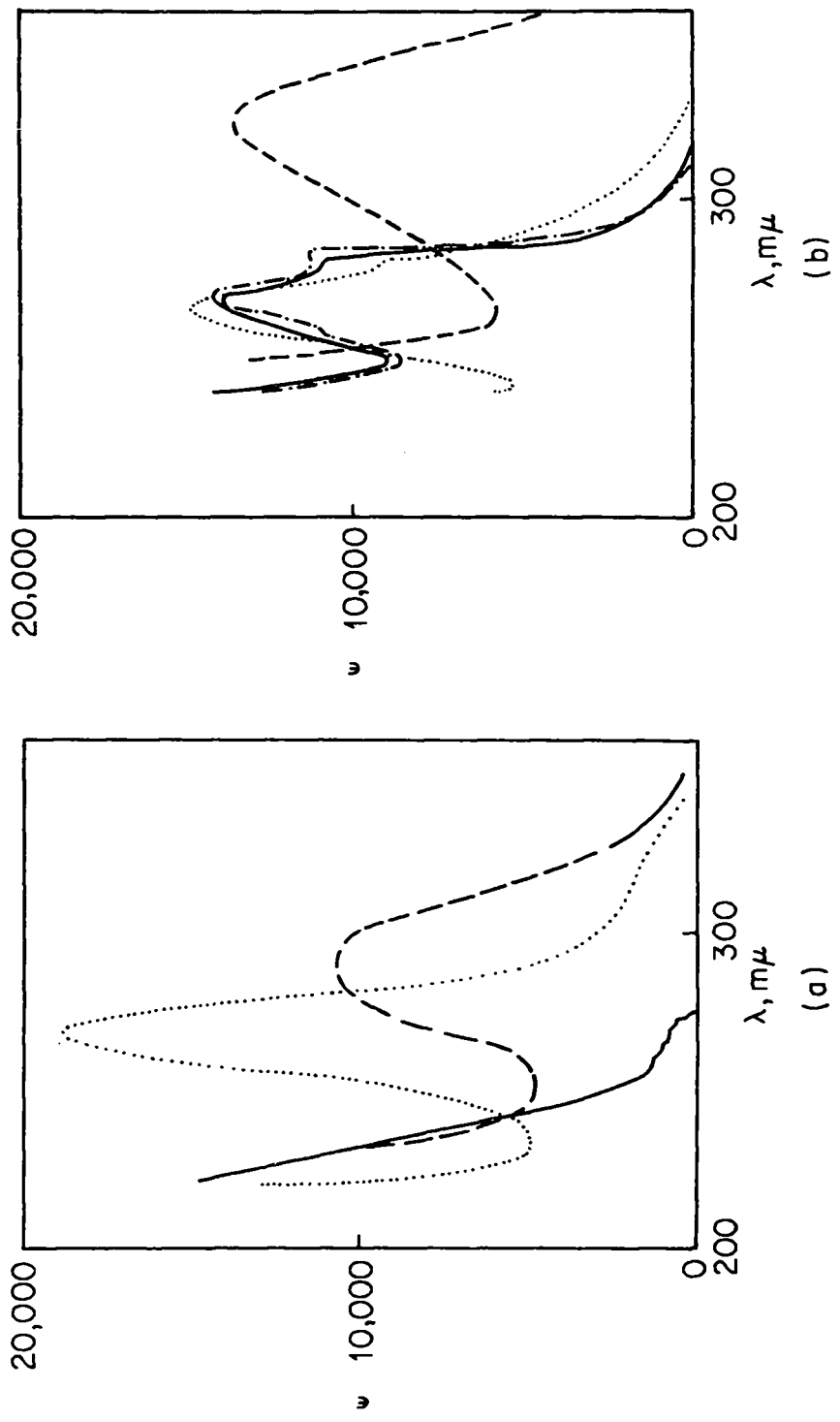
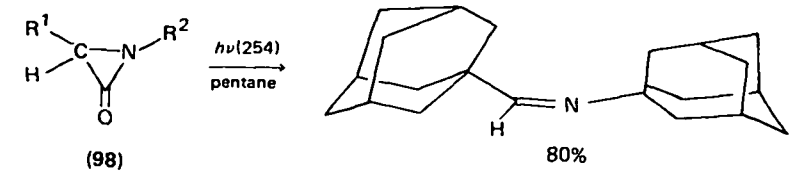
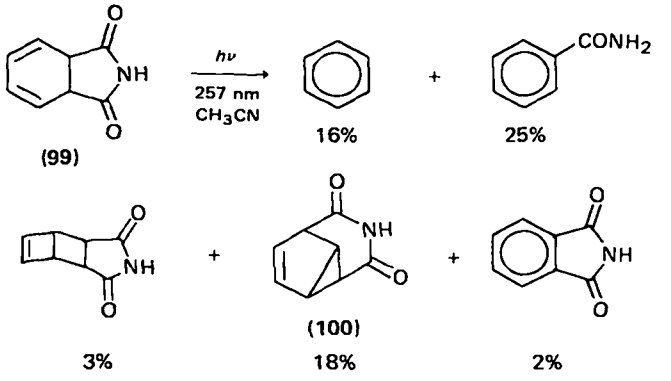


FIGURE 6. U.v. spectra in EtOH of (a) **88**, (b) **89**; X = H (——), X = NMe_2 (· · · ·), X = NO_2 (— — —). Taken from W. A. Henderson, Jr. and A. Zweig, *Tetrahedron*, **27**, 5307 (1971). Reproduced by permission of Pergamon Press.



(98)
($R^1 = R^2$ = adamant-1-yl)

(39)



(99)

(100)

(40)

account for the major products of photolysis of 1,2-dihydrophthalimide (**99**). The unusual rearrangement product **100** will be discussed in Section VI. The imide reaction was also shown to be a singlet reaction[56b]. These two reactions illustrate the photoreactivity of the nitrogen analogues of anhydrides and lactones but only these few studies have been reported. Future investigations seem inevitable.

IV. PHOTODECARBOXYLATION

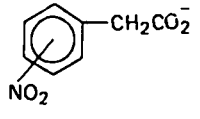
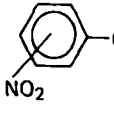
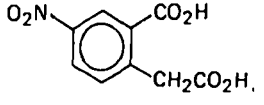
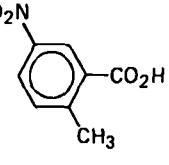
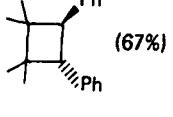
One of the most common photochemical reactions of carboxyl derivatives is decarboxylation. As indicated in the following sections, the nature of the carboxyl group (i.e. carboxylate, carboxyl or ester group) and the substituents attached influence the efficiency of the decarboxylation process as well as the chemical fate of the intermediates generated by the loss of carbon dioxide. Since the photodecarboxylation studies of acids and their salts richly illustrate the variety of reactions and the importance of reaction conditions, this area will be considered first.

A. Acids

As Table 5 illustrates, a wide variety of organic acids have been examined for their photochemistry. For each of the entries in the Table, carbon dioxide has either been trapped or assumed to be produced from the nature of the other products obtained. The efficiency of the decarboxylation reaction and the types of products obtained depend largely on three parameters: (*i*) the structure of the reactant (aliphatic, aryl or aryl methyl carboxylic acid), (*ii*) the presence or absence of oxygen and (*iii*) whether the reactant is the free acid or its conjugate base.

Early reports[92] on the photochemistry of aliphatic carboxylic acids were principally confined to gas-phase studies. Formic acid was shown to yield four products

TABLE 5. Photodecarboxylation of acids

Acid (salt)	Conditions[a]	Products (yields)	Reference
(101) HCO_2H	Hg, quartz	CO_2, H_2, H_2CO, CO	59a, 92
(102) CH_3CO_2H	H_2O, 200–240 nm	CO_2, (see text)	59b, 60a, 68, 81
(103) $HO_2C(CH_2)_nCO_2H$ $n = 1, 2$		CO_2, ($n = 2$, C_2H_6, CH_4, CH_3CO_2H) ($n = 1$, CH_3CO_2H, CO, H_2, H_2O)	59, 60a, 81, 82
(104) $PhCH_2CO_2H$	Glass, 77 K also solution (see text)	CO_2, toluene, bibenzyl (also see text)	60b, 64, 75, 82, 91, 93
(105) $CH_3CH_2CH_2CO_2H$	Hg, base, H_2O	CH_2CH_2, CH_3CO_2H, HCO_3^-	61, 59b
(106) $(CH_3)_2CHCO_2H$	Hg, base	HCO_3^-	61
(107) CH_3COCO_2H	>280 nm, H_2O, other solvents	CO_2 (85%), $CH_3CHOHCOCH_3$ (85%)	62, 63
(108) $PhCOCO_2H$	>310 nm, H_2O	CO_2 (Φ, 0.79), PhCHO (60%)	63
(109) *o*, *m*, *p* 	Flash *hv*, H_2O, B^- and Hg, hp, monochromator Pyrex, H_2O	CO_2,  (Φ_o, 0.04; Φ_m, 0.63; Φ_p, 0.59)	65, 67
(110) 	Flash *hv*, H_2O, B^- and Hg, hp, monochromator Pyrex, H_2O	CO_2 (Φ, 0.60), 	65, 67
(111) 2,4-Dinitrophenylacetic acid	Flash *hv*, H_2O, B^- and Hg, hp, monochromator Pyrex, H_2O	CO_2, (Φ, 0.04), 2,4-dinitrotoluene	65, 67
(112) 4,4′-Dinitrodiphenylacetic acid	Flash *hv*, H_2O, B^- and Hg, hp, monochromator Pyrex, H_2O	CO_2, 4,4′-dinitrophenyl methane	65, 67
(113) 2-Phenylcinnamic acid (*cis* and *trans*)	Hg, mp, quartz, CO_2, ether, 	 (67%)	66

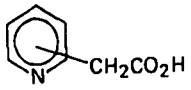
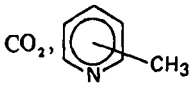
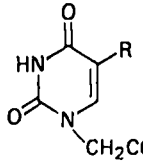
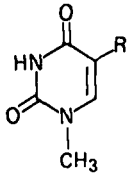
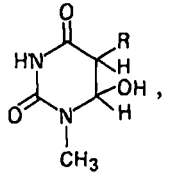
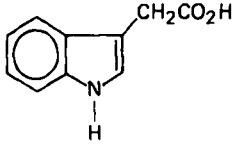
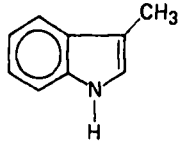
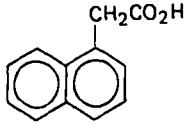
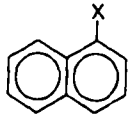
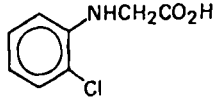
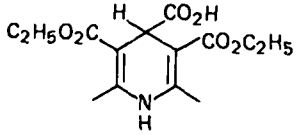
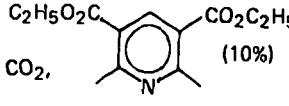
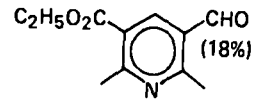
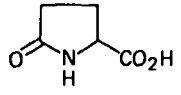
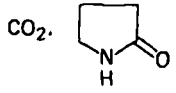
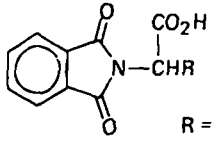
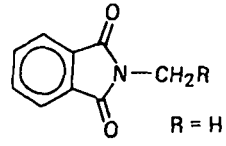
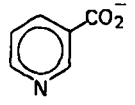
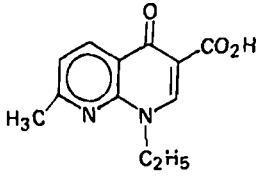
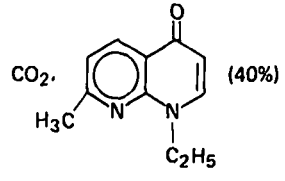
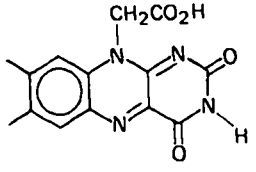
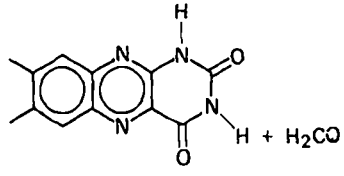
(114) *o*, *m*, *p* 	ether, Hg, 1p, quartz, H_2O	CO_2,  (Φ_o, 0.48; Φ_m, 0.45; Φ_p, 0.19)	69
(115)  R = H, CH_3	Hg, 1p, quartz, H_2O	 ,  CO_2	70
(116) 	Hg, 1p, quartz, H_2O	CO_2, 	71
(117) 	254 nm, O_2, H_2O	CO_2,  (X = CH_3, CH_2OH, CHO)	72, 73
(118) $PhCO_2H$	Hg, vapour phase	CO_2, benzene, CO	74
(119) 	Hg, 310 nm, $ArNO_2$ as sensitizer CH_3CN	CO_2, *N*-methyl-2-chloroaniline (30–40%)	76
(120) $PhXCH_2CO_2H$ (a) X = S (b) X = O (c) X = NH	Hg, 350 nm, Pyrex, benzene Ph_2CO sensitizer	CO_2, PhXH, $PhXCH_3$, (see text)	76, 85, 93
(121) *n*-$BuNHCH_2CO_2H$	Hg, 350 nm, Pyrex, benzene, Ph_2CO sensitizer	CO_2, *n*-$BuNH_2$	76
(122) $CH_3CCl_2CO_2H$ (Φ_d = 0.89)	Hg, 1p, 254 nm, quartz, H_2O, 49°C, O_2	CO_2 (Φ, 0.46), Cl^- (Φ, 1.54), CH_3COCO_2H (Φ, 0.14), CH_3CHO (Φ, 0.15), CH_3CHCl_2 (Φ, 0.01)	77

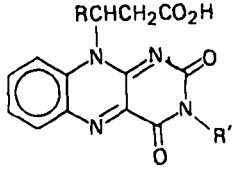
TABLE 5. (Continued)

Acid (salt)	Conditions[a]	Products (yields)	Reference
(123) 	254 nm, quartz, *t*-BuOH	CO_2,  (10%)  (18%)	78
(124) 	Hg, hp, quartz, H_2O	CO_2, 	79
(125)  R = H, others	Hg, hp, acetone,	CO_2,  R = H (80%)	80
(126) $PhCHOHCO_2H$	Hg, 254 nm, H_2O or EtOH	CO_2, PhCHO, $PhCH_2OH$, $(CO_2H)_2$, PhCHOHCHOHPh	82
(127)  Nicotinic acid	Hg, 254 nm, EtOH	CO_2, pyridine	83
(128)  Nalidixic acid	Hg, quartz, NaOH, H_2O	CO_2,  (40%)	84

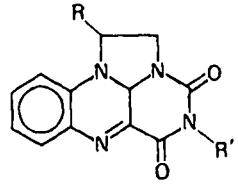
(129) 

9,10-Dimethylisoalloxazine-10-acetic acid

Hg, 420–450 nm filter, H_2O CO_2,  86

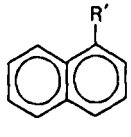
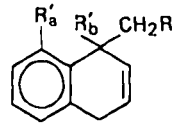
(130) 

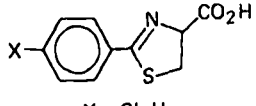
R = H, R′ = CH_3
R = R′ = CH_3

Hg, mp 420–450 nm filter, H_2O CO_2,  86

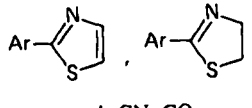
(131) RCH_2CO_2H
R = *p*-$CH_3OC_6H_4$, *m*-$CH_3OC_6H_4$, C_6H_5, *p*-$CH_3C_6H_4$

Hg, mp, Corex, CO_2, RCH_3, $(RCH_2)_2$, 87

CH_3CN,  (R′ = CN, OCH_3)  (R'_a = OCH_3, R'_b = CN)

(132) 

X = Cl, H

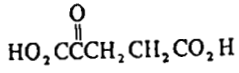
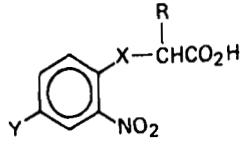
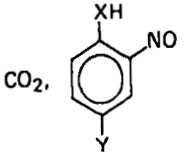
254 nm, CH_3CN  88

ArCN, CO_2

(133) $CF_3CO_2^-$ Ag^+

Hg, Hp, quartz, benzene CO_2, $PhCF_3$ (57%) 89

TABLE 5. (Continued)

Acid (salt)	Conditions[a]	Products (yields)	Reference
(134) 	Potassium chromate filter solution, Rose Bengal or methylene blue, MeOH, CH_3CN and/or pyridine	CO_2, no other products identified	90, 221
(135)  X = O, NH Y = H, NO_2	Hg, mp, O_2, H_2O	CO_2, 	97, 98

[a]See Table 3 for format.

as illustrated in equation (41). The product distribution[92b] has been shown to depend on the association of the acid. For the dimeric acid ($x = 2$), the major product was CO_2, while for the monomeric acid, CO and CO_2 are both major products, occurring in a ratio of 2:1.

$$(HCO_2H)_x \xrightarrow[\text{gas phase}]{h\nu\,(200-254)} CO_2 + H_2 + CO + H_2O \qquad (41)$$

Studies on acetic acid by Ausloos and Steacie[92d] extended the general processes to higher analogues. Earlier, Farkas and Wansbrough-Jones[59b] had shown that monomeric acetic acid decomposed by decarboxylation whereas the dimeric form gave both CO and CO_2, in direct contrast to formic acid photolysis. In the more recent study[92d], however, no dependence on the degree of association was found.

Although several investigators had reported that the solution irradiations of simple aliphatic carboxylic acids yield chiefly carbon dioxide[59,60a,61,68], no systematic studies on the nature of these reactions were available until those of Mittal, Mittal and Hayon appeared[81]. Flash photolysis of oxygen-free aqueous solutions of acetic acid produced a transient absorption due to the CO_2H radical. Its formation was pH dependent, being most efficient at low pH. A 'titration-type' curve indicated a $pK = 4.65 \pm 0.1$ for the production of $\cdot CO_2H$, in good agreement with the pK_a of acetic acid (4.76). This pH dependence is evidence that initial rupture of the $H_3C{-}CO_2H$ bond (fragmentation *a*, Figure 5) is a primary mode for photodecomposition of the acid. The CO_2H radical subsequently loses a hydrogen atom to yield CO_2. The other major product of this reaction, methane, presumably arises from the methyl radical generated in the same initial homolysis step. Equation (42) shows the sequence suggested[81].

$$CH_3CO_2H \xrightarrow[>200\,nm]{h\nu} CH_3\cdot + \cdot CO_2H \longrightarrow CH_4 + CO_2 \qquad (42)$$

Although no transients have been observed at higher pH, the photodecomposition of acetate salts nevertheless does occur under these conditions[59b]. The products of the reaction are CO_2 and methane as well as methanol and formic acid (equation 43). The mechanism for their formation is not known, however.

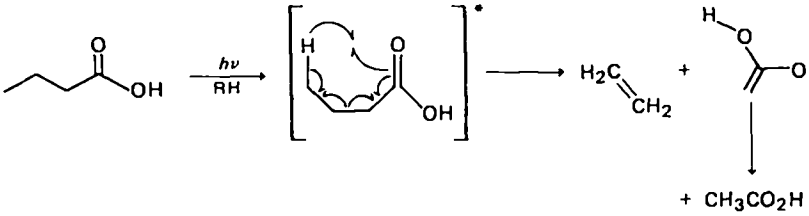
$$CH_3CO_2^- \xrightarrow[H_2O]{h\nu} CH_4 + CO_2 + CH_3OH + HCO_2H \qquad (43)$$

Mittal, Mittal and Hayon[81] were able to discount the intermediacy of $\cdot CO_2^-$, e_{aq}^-, and $\cdot CH_2CO_2H$, since no transient spectra for these known radicals were observed. For the aryl carboxylate salts, these authors have found that flash excitation of the aryl chromophore produces solvated electrons by a biphotonic process. The electron is ejected from the carboxylate group since the corresponding esters neither produced the solvated electron nor gave the same primary cleavage reactions[81].

Attempts to assign the dissociative excited state for CH_3CO_2H as either singlet or triplet have been inconclusive. Attempted quenching experiments for malonic acid (**103**, $n = 1$) employing $Ni(ClO_4)_2$ resulted in no change in production of $\cdot CO_2H$ or $\cdot CH_2CO_2H$ radicals[81]. Gas-phase mercury sensitization experiments[92e,f] enhanced the rate of formation of both CO_2 and CO, particularly the latter, in the study of formic acid. Thus, either the excited-state precursor is a short-lived triplet or the singlet excited state of the acid (diacid).

When the length of the carbon chain attached to the carboxyl group increases to three or more, another primary photochemical process competes with cleavage of the carboxyl carbon–carbon bond. Borrell and Norrish[61] have shown that the *type II* process (see Section V.B) occurs for butyric acid (**105**) and its derivatives. Thus,

in addition to propane, hexane and propene, the products arising from decarboxylation, large quantities of ethylene were formed. These authors suggested that the *type II* process (equation 44), analogous to that established for ketones, was

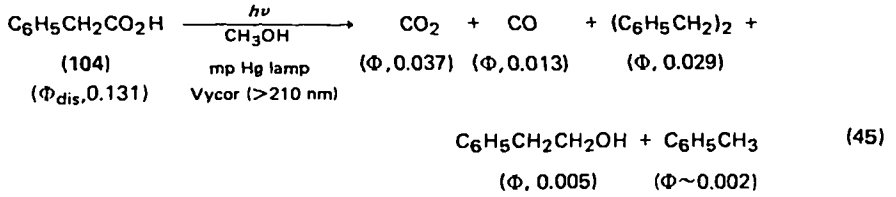


(44)

occurring. Attempts to sensitize (Hg) this reaction were not definitive though CO_2, CO, and propane were found in the product mixture. No ethylene was formed, however, suggesting that the singlet state is the predecessor to the γ-hydrogen abstraction while the triplet state of the acid undergoes decarboxylation. (However, see Section V for a detailed discussion of hydrogen abstraction reactions.)

As the degree of substitution on the carbon chain becomes more complex, the photochemistry changes also, often becoming very complex. Three notable substitution patterns warrant further discussion, however, due to the absence of complicating side-reactions and secondary pathways upon decarboxylation. These are: (*i*) the aryl acetic acids, (*ii*) the ArX derivatives (X = O, S, NH, etc.) of acetic acid and (*iii*) α-keto acids. In all cases, the absorbing chromophore includes the substituent. However, the photodecarboxylation reaction is the chief pathway for the excited-state chemistry.

Of the first group of acids, phenylacetic acid (**104**) has received considerable attention[60,64,75,82,91]. Meiggs and Miller[75] have examined the photochemistry in detail, identifying the five products that are shown in equation (45). It is



(45)

apparent from the disappearance efficiency and the product-appearance quantum yields that 50 per cent of the material was not identified. An acidic polymer was also obtained, though not characterized further. Earlier studies by Porter and Strachan[60b] and by Grossweiner and Joschek[64,93] employing flash techniques detected a strong 318 nm transient assigned as the absorption band of the benzyl radical. In the latter study at pH 8.4 absorption due to solvated electrons was also registered, suggesting a sequence like that given in equations (51a) and (52) in Scheme 5 for phenylacetate salts. For the acid, the principal sequence would be steps (46)–(49). Carbon monoxide formation, which is not explained by this sequence, requires cleavage of the RCO–OH bond (bond *b*, Figure 5) followed by decarbonylation.

The major hydrocarbon products from alcohol solution studies are bibenzyl and toluene. The bibenzyl formation is perhaps the strongest evidence that benzyl radicals are formed in high yield, while toluene probably arises from the benzyl anion[75b]. A pH study on the photochemistry of phenylacetic acid has not been done, largely due to the complications arising from the insolubility of the products,

$$ArCH_2CO_2H \xrightarrow{h\nu} [ArCH_2CO_2H]^1 \quad (46)$$

$$[ArCH_2CO_2H]^1 \longrightarrow ArCH_2\cdot + \cdot CO_2H \quad (47)$$

$$\cdot CO_2H \xrightarrow{M} MH + CO_2 \quad (48)$$

$$2\,ArCH_2\cdot \longrightarrow (ArCH_2)_2 \quad (49)$$

$$ArCH_2CO_2^- \xrightarrow{h\nu} [ArCH_2CO_2^-]^* \quad (50)$$

$$[ArCH_2CO_2^-]^* \longrightarrow ArCH_2CO_2\cdot + e^- \quad (51a)$$

$$[ArCH_2CO_2^-]^* \longrightarrow ArCH_2^- + CO_2 \xrightarrow{ROH} ArCH_3 \quad (51b)$$

$$ArCH_2CO_2\cdot \longrightarrow ArCH_2\cdot + CO_2 \quad (52)$$

SCHEME 5. Photodecarboxylation of arylacetic acids and arylacetate salts.

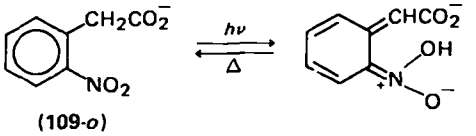
particularly bibenzyl. However, a very recent labelling study by Epling and Lopes[91] in mixed isopropyl alcohol–water and methanol–isopropyl ether solutions does provide some information on the intermediates from the free acid and its salt. With the excellent hydrogen-atom source present, toluene is the major product. By varying the isotope of hydrogen available for abstraction, Epling and Lopes were able to show that the acid decomposes to the benzyl radical, whereas the sodium salt forms toluene via the benzyl anion (equation 53). Since attempts to sensitize or

$$PhCH_2CO_2^-Na^+ \xrightarrow[H_2O-1\%\,(CH_3)_2CDOH]{h\nu\ (254\ nm)} \underset{95\%}{PhCH_3} + \underset{5\%}{PhCH_2D} + CO_2 \quad (53)$$

quench these reactions failed, the multiplicity for the decarboxylation step is probably the singlet state[91].

A systematic substituent-effect study on the photodecarboxylation reaction of phenylacetic acids has not been performed although several nitrophenylacetate ions were examined by Margerum and coworkers[65,67]. *Meta*- and *para*-nitro substitution enhance the efficiency for decarboxylation of the conjugate base as evidenced from the entries in Table 6. However, the *ortho*-substituted acids photodecarboxylate with only moderate efficiency. Product analysis for the nitrophenylacetates reveals that the corresponding toluenes are produced, except in the case of sodium *p*-nitrophenylacetate (**109**-*p*). For **109**-*p*, only 7–9% of *p*-nitrotoluene is formed whereas 71–78% of the *p,p'*-dinitrobibenzyl is produced.

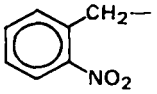
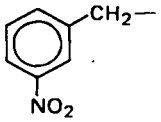
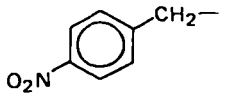
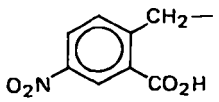
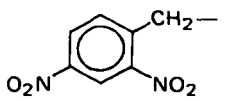
Flash photolysis of these nitrophenylacetic acids gave transients assigned to the nitrobenzyl anion for **109**-*o* and **109**-*p*. In addition, the *ortho* isomer produced a long-lived ($\tau = 830$ ms) transient absorbing at 408 nm due to the abstraction of the α'-hydrogen as shown in equation (54). This reversible process can be considered an



(109-*o*) (54)

energy wastage step[94] and may account in part for the lower efficiency of the decarboxylation process for **109**-*o*. A similar explanation would account for the

TABLE 6. Quantum efficiencies for photodecarboxylation of substituted arylacetic acids (RCO_2H) in H_2O at 367 nm

	Substituent (R)	Φ_{CO_2} $-CO_2^-$	Φ_{CO_2} $-CO_2H$	Reference
(104)	$PhCH_2-$	0.009[a]	0.037[b]	67, 75
(109-*o*)		0.04	*c*	67
(109-*m*)		0.63	0.00	67
(109-*p*)		0.59	0.00	67
(110)		0.60	*c*	67
(111)		0.04	*c*	67

[a]254 nm.
[b]Methanol.
[c]Not determined.

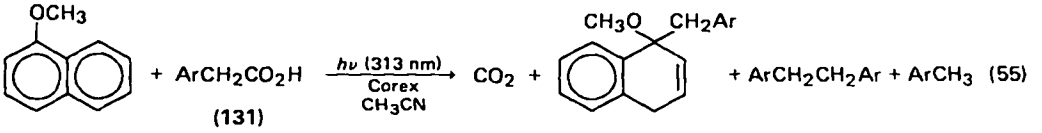
lower efficiency for 2,4-dinitrophenylacetic acid (**111**). To attribute a more involved mechanistic explanation to the substitution pattern[7,15] would be premature.

However, a clear example of the effect of substitution can be found in the pyridylacetic acids (**114**, Table 5) where intramolecular hydrogen abstraction is not possible[69]. All three derivatives photodecarboxylate readily to give the methylpyridines, a reaction which for **114**-*m* is not quenched by oxygen or biacetyl. Attempted sensitization with acetone was successful but the authors[69] believed that singlet energy transfer had occurred (see Table 1). Thus a singlet mechanism is suggested. If all three react via the same manifold and since all three give the same type of products (methylpyridines) and have similar spectra, a rough comparison of substituent effects is possible*. The relative order of reactivity of the carboxylate ions **114**-*o*: -*m*: -*p* is 5:5:2. This *o*-, *m*- enhanced reactivity is reminiscent of the photosolvolysis results found by Zimmerman[15] and Havinga[95].

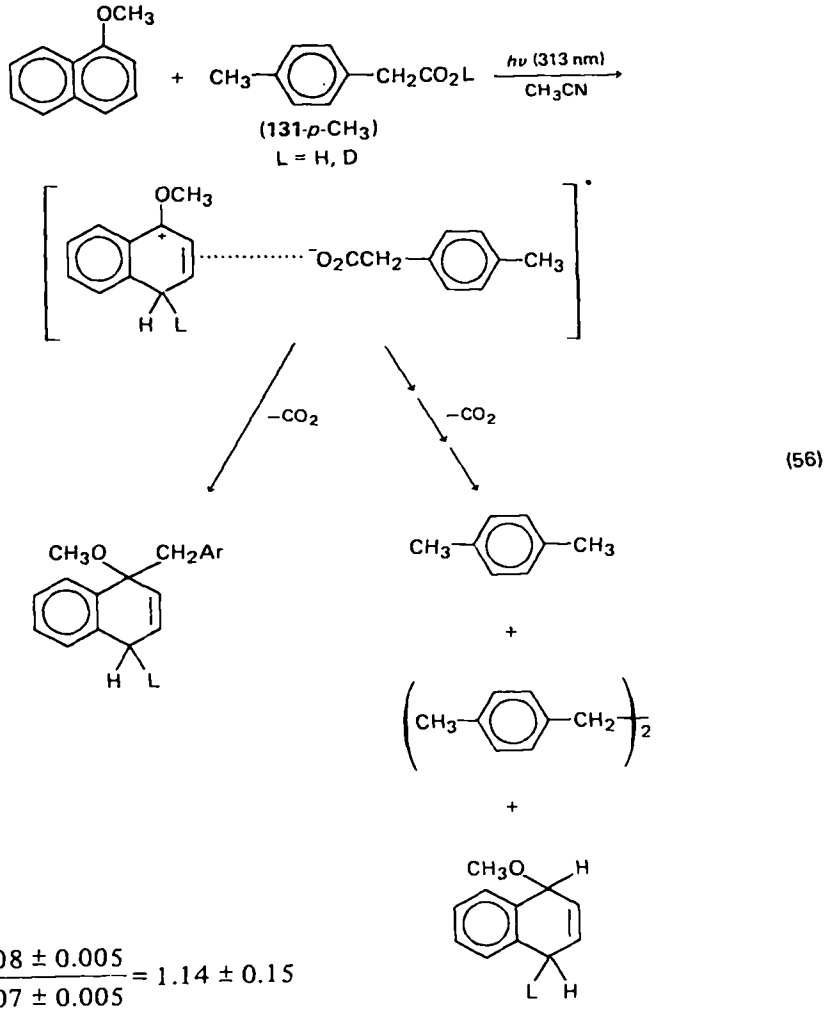
Related studies by Libman[87] of substituted phenylacetic acids show a reasonably good linear Hammett correlation ($\rho = 1.0$) for the substituent effect on the

*Ideally, individual rate constants would be used for such an analysis (see Section II).

efficiency of photoreaction of 1-methoxynaphthalene with substituted phenylacetic acids. The reaction leads to several products, a major one resulting from the addition of the decarboxylated benzyl group to 1-methoxynaphthalene (equation 55). The naphthyl derivatives serve a dual purpose as both sensitizer and



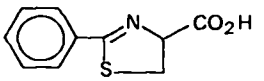
reactant, complicating the delineation of the origin of the substituent effect (e.g. energy-transfer rates to **131**). Nevertheless, the correlation does suggest that the decarboxylation involves an initial proton-transfer step followed sequentially by decarboxylation and alkylation. In accord with this view, Libman found a small isotope effect on the reaction of 1-methoxynaphthalene with *p*-tolylacetic acid-d (equation 56).



$$\frac{k_H}{k_D} \approx \frac{\Phi_H}{\Phi_D} = \frac{0.08 \pm 0.005}{0.07 \pm 0.005} = 1.14 \pm 0.15$$

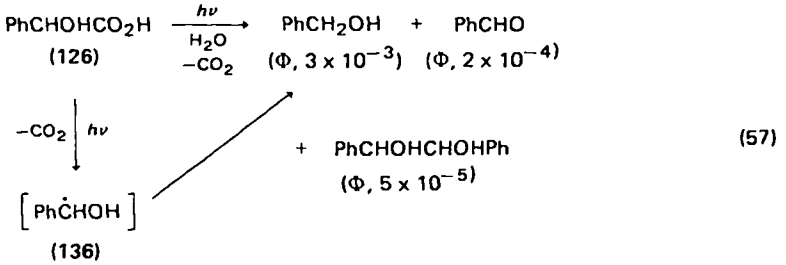
Using acridine as the sensitizer and reactant, substituted phenylacetic acids react by reductive alkylation to form 9-substituted acridines in yields of 50% to 80% with efficiencies of 0.2 to 0.3 for most substituents. CIDNP studies of this reaction revealed the intermediacy of a radical pair consisting of the benzyl radical and the protonated acridyl radical cation. The evidence is consistent with a sequence which involves (*i*) protonation of acridine's excited singlet, (*ii*) electron transfer from the carboxylate moiety to the acridyl ion ($\rho = +$), (*iii*) decarboxylation of the carboxyl radical to a caged benzyl, protonated-acridyl radical pair followed by (*iv*) radical coupling processes (cage and non-cage)[87]. Although other mechanisms are possible, this route is consistent with all of the studies reported by Libman.

Several other arylacetic acid derivatives of biological significance photocarboxylate efficiently. Some examples, given in Table 5, include pyrimidines (**115**), indoleacetic acid (**116**) and naphthylacetic acids (**117**). 1-Naphthylacetic acid, for example, has frequently been employed as a plant growth regulator. However, its effectiveness is substantially reduced when it is exposed to intense sunlight. Watkins[72] and Crosby and Tang[73] showed that photodecarboxylation converted **117** to a mixture of inactive 1-naphthyl derivatives. Izawa and coworkers[88] have shown that 2-phenyl-Δ^2-thiazoline-4-carboxylic acid (**132**), which is structurally related to firefly luciferin, affords photodecarboxylation products upon irradiation at 254 nm. Structurally, these are vinylogues of the phenylacetic acids.



(132)

Substitution at the α-carbon of phenylacetic acid does not alter the reaction pathway, as shown by studies on mandelic acid (**126**)[82]. The products, which are shown in equation (57), arise from an initial, inefficient photodecarboxylation



(57)

step to form the α-hydroxybenzyl radical **136**. This either couples or disproportionates to give the expected products of **136**. Addition of azo dyes increases the apparent efficiency of photodecomposition by trapping the initially formed radicals. The quantum efficiencies for formation of benzaldehyde and benzyl alcohol increase (0.083 and 0.065, respectively), while hydrobenzoin formation is almost eliminated.

The second group of acid derivatives which has been studied in detail has the general structure $R\ddot{X}CH_2CO_2H$ where $\ddot{X}$ is either N, O or S. Entries **119**–**121**, **124**, **125** and **135**, Table 5, are representative of this class of compounds. Davidson, Steiner and coworkers[76,96] have shown that photodecarboxylation of $PhXCH_2CO_2H$ (where X = O, NH or S) can be effected by a number of triplet sensitizers. Table 7 lists the results with a number of the sensitizers investigated when

TABLE 7. Sensitized irradiations of $RXCH_2CO_2H$[96a]

Sensitizer	% Yield of $RXCH_3$ (% CO_2)[a]			
	$PhOCH_2CO_2H$	$PhSCH_2CO_2H$	$ArNHCH_2CO_2H$[b]	n-$BuSCH_2CO_2H$
Benzophenone	50 (50)	50 (49)	84 (53)	100 (37)
9,10-Anthraquinone	50 (47)	48 (45)	31 (11)	96 (37)
9,10-Phenanthraquinone	11 (11)	20 (31)	9 (11)	trace (5)
Tetrachloro-*p*-benzoquinone	0 (40)	3 (44)	2.4 (42)	0 (18)
p-Benzoquinone	0 (9)	– (27)	– (48)	– (10)

[a]Thiophenol present as a hydrogen-atom donor.
[b]Ar = *o*-chlorophenyl.

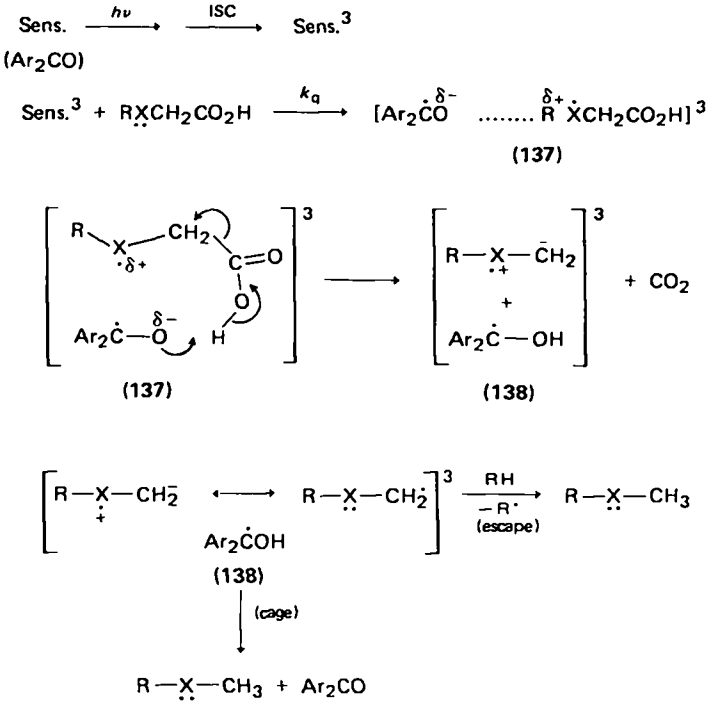
added thiophenol is the hydrogen-atom source. Yields of the decarboxylated aryl ethers were substantially lower when thiophenol was absent. In contrast, carbon dioxide yields were higher when the hydrogen donor was absent. Quenching and photoreduction of the sensitizer by thiophenol in competition with excited-state complexation with **119–121** also occurs thus reducing the efficiency of the reaction. In spite of this added complication, many of the compounds could be decarboxylated in reasonable yields (conversions of ca 50%) with benzophenone as the sensitizer, enhancing the synthetic potential of the reaction. Product yields, corrected for recovery of starting ester were nearly 100% in all cases[96a].

The mechanism of this photodecarboxylation has also received considerable attention [76,85,96]. The initial step is formation of an excited sensitizer–reactant intermediate, the nature of which is dependent on the type of reactant. For (phenylthio) acetic acid, Davidson and Steiner[76b] consider the intermediate to be a triplet exciplex (**137**) with substantial charge transfer from the heteroatom to the sensitizer. Electron transfer is followed by proton transfer, which in turn leads to the decarboxylation as shown in Scheme 6. (However, CIDNP studies[85] failed to confirm the presence of the intermediate **137**.) The decarboxylated radical pair **138** then either disproportionates, or the radicals escape the cage and abstract a solvent-bound hydrogen to form the product. This last combination of steps gives rise to the CIDNP signals shown in Figure 7[85a]. The methyl protons show enhanced emission (E)* when the sensitizer serves as the hydrogen-atom source for **13**, i.e. $\Gamma_{NE} = \mu\epsilon\Delta g A_i = +++- = -(E)$[99]. Enhanced emission is observed when benzophenone, fluoren-9-one or phenazine is used as sensitizer (Figure 7, la and b). Separation of the geminate pair **13** followed by hydrogen-atom abstraction leads

*An excellent discussion and analysis of CIDNP effects may be found in Reference 99.

The symbols used here are those defined by Kaptein[99] as: E = enhanced emission (–) and A = enhanced absorption (+) from the net polarization (Γ_{NE}) of an n.m.r. signal resulting from sample photolysis. The parameters that determine the net polarization are: μ = the multiplicity of the radical pair [singlet (–) or triplet (+)], ϵ = cage (+) or non-cage (–) combination of the radical pair, Δg = g-factor difference between the two reacting radicals and A_i = hyperfine coupling constant of the hydrogen (+ or –).

The Kaptein equation allows the *determination of any one of these parameters, when the other three are known*. In most cases, Δg and A_i are known, allowing access to the nature of the reaction (cage vs non-cage) or the multiplicity of the radical pair by this technique.



SCHEME 6. Photosensitized decarboxylation of $RXCH_2CO_2H$.

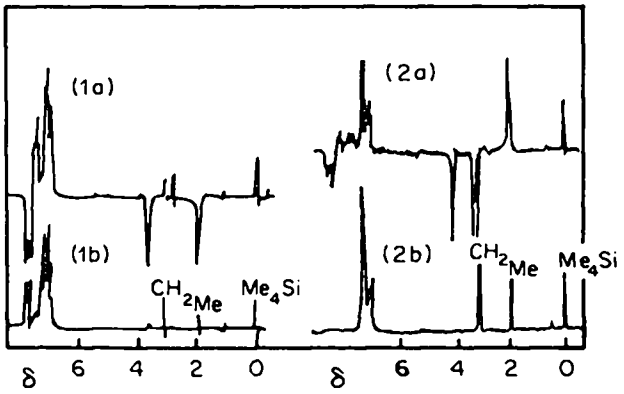


FIGURE 7. 90 MHz ^{1}H n.m.r. spectra (a) during irradiation with a 1000 W Hg–Xe lamp, (b) following irradiation. (1) (Phenylthio) acetic acid and benzophenone, both 0.1 M, in C_6D_6, Me_4Si standard; (2) same as (1) but anthraquinone (saturated solution) used as sensitizer. Taken from M. Weinstein, K. A. Muszkat and J. Dobkin, *J. Chem. Soc., Chem. Commun.*, 68 (1975). Reproduced by permission of the Chemical Society, London.

to enhanced absorption [ϵ = −, other terms unchanged, Γ_{NE} = +(A)]. Enhanced absorption (A) is observed for anthraquinone and duroquinone in C_6D_6 and by benzophenone in C_6D_6 when thiophenol is added (Figure 7, 2a and b).

The observation of enhanced emission from the methylene protons of (phenylthio)acetic acid (**120**) is not consistent with the triplet exciplex (**137**) postulate of Davidson and Steiner[76b] where A_i = +25 G[100] and Γ_{NE} = ++++ = +(A). Instead, this signal probably results from a process like disproportionation or recombination of geminate pairs such as [PhSCHCO$_2$H · · · ·Sens–H] or [PhSCH$_2$ · · · · ·CO$_2$H]. If a triplet exciplex is involved, it must have a very short lifetime[81,85].

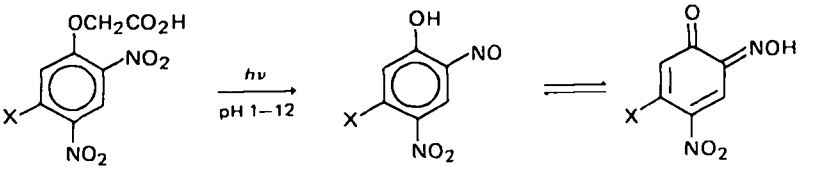
Support for the exciplex mechanism of Davidson and Steiner[76,96c] is derived from the correlation of the rate constants for benzophenone-sensitized decarboxylation of RXCH$_2$CO$_2$H with the rate constants for quenching of benzophenone by certain sulphides and amines. The rate constants for decarboxylation are derived from Stern–Volmer plots for naphthalene quenching of the reaction (equation 61).

$$\Phi/\Phi_q = 1 + k_q[\text{Naph}]/(k_d + k_r[\text{acid}]) \tag{61}$$

Employing the values of 5×10^9 M^{-1} s^{-1} and 3×10^5 s^{-1} for k_q and k_d[101], respectively, the k_r ($\times 10^{-8}$) values obtained for **119**, **120a, b** and (*n*-butylthio)-acetic acid were 21, 1.0, 0.17 and 1.6 M^{-1} s^{-1}. These values are comparable to the rate of exciplex formation of benzophenone with methyl phenyl sulphide, di-*n*-butylsulphide and *N*,*N*-dimethyl aniline, k_q ($\times 10^{-8}$) = 0.75, 6.6 and 27 M^{-1} s^{-1}, respectively, from Cohen's studies[102]. Furthermore, the similarity in the k_r values for (phenylthio)acetic acid and (*n*-butylthio)acetic acid are consistent with an electron-transfer, exciplex formation.

Rate constants (k_r) determined in this way are not direct measures of the rate of decarboxylation but are more properly termed rate constants of sensitization, i.e. they are a measure of the energy-transfer rate for the sensitizer. The fact that the transfer step was shown to be independent of the presence or absence of the carboxyl group can be taken as evidence for a similar energy-transfer step, however. Furthermore, the absence of exciplex formation and photosensitized decarboxylation from alkoxyacetic acids and aliphatic amino acids which have high ionization potentials (>9eV) supports this mechanism[76].

Certain *N*-aryl α-amino acids are known to photodecarboxylate[98]. Most notable are the *o*-nitroaryl derivatives **135**[98]. The photodecarboxylation is accompanied by reduction of the *ortho*-nitro group, yielding either a benzimidazole-*N*-oxide at low pH or a nitroso aniline at high pH. McFarlane and Russell[97] have extended this latter reaction to the corresponding phenoxyacetic acids (equation 62). For this system, no pH dependence was observed.



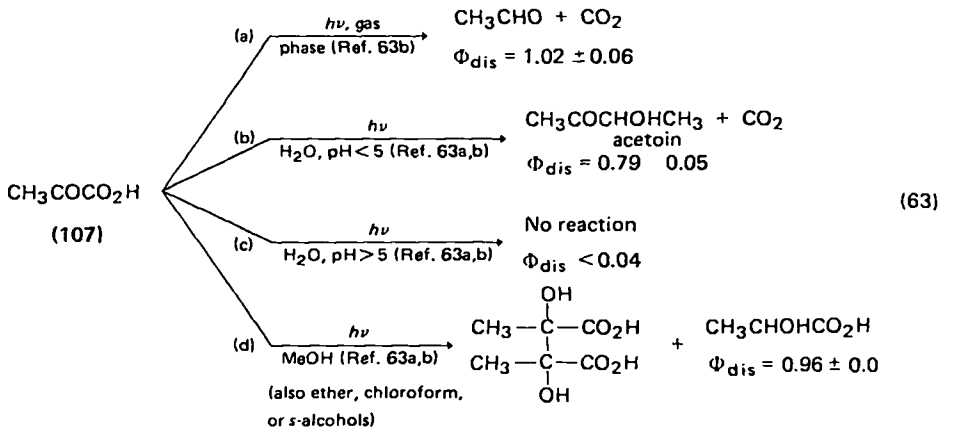
(62)

(135)

X = H, OCH_3, OC_2H_5, OC_3H_7, O-*i*-C_3H_7, O-*n*-C_4H_9 and O-*i*-C_4H_9

The last group of carboxylic acids to be discussed which photodecarboxylate relatively efficiently are the α-keto acids[62,63,81,90]. Leermakers and Vesley[62,63a,b,c] have shown that irradiation of pyruvic acid (**107**) in aqueous solution leads to photodecarboxylation with high efficiency ($\Phi = 0.79$). Under identical conditions, sodium pyruvate was unreactive. Flash photolysis studies[81] revealed the presence of a short-lived transient absorption from ~350 to 270 nm, which was assigned to both the $\cdot CO_2H$ and the $CH_3CO\cdot$ radicals. This transient was observed at low pH but practically disappeared at higher pH, a trend that was noted earlier for other aliphatic acids (*vide supra*). The pH dependence was only one manifestation of the medium dependence that this reaction displayed. Equation (63) illustrates the effect of 'solvent' change on the nature of the products obtained. The high quantum yields emphasize the point that fundamental changes in reaction pathways take place as reaction conditions are altered. Thus, photoreduction of the ketone carbonyl in hydrogen-atom donating solvents (equation 63d) must be occurring at a relatively rapid rate to completely dominate the photodecarboxylation process (equations 63a, b). The photoreduction reactions to tartaric acid derivatives are readily explained as normal behaviour of n--π^* ketone photoreductions, having been discovered much earlier for **108** by Schönberg and coworkers[103].

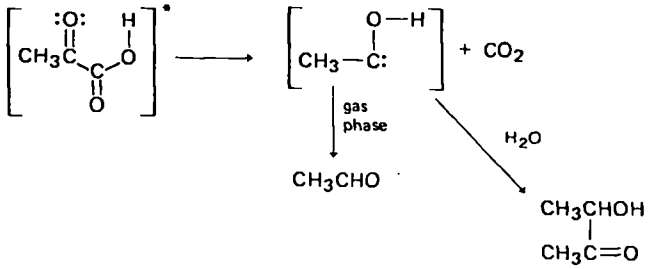
When hydrogen-atom donating solvents are absent, photodecarboxylation may take place under appropriate conditions. Leermakers has reported that no photodecomposition was noted for pyruvic acid in benzene[62] or for the sodium salt in water[63a] but highly efficient loss of CO_2 was observed in the gas phase[63b,d] and in water[62,63a]. The difference in the products for these last two studies is also interesting (equation 63a, b) The gas-phase study afforded acetaldehyde, which can



(63)

(Φ_{dis} is the quantum efficiency for disappearance of pyruvic acid, measured spectrophotometrically)

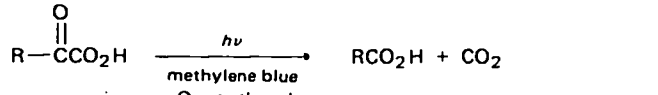
be rationalized in terms of an intramolecular hydrogen shift followed by decarboxylation and further hydrogen migrations as shown in equation (64)[63d]. The proposed intermediacy of the hydroxycarbene is unusual, though its rearrangement to the acetaldehyde would be expected. No precedence exists for this process, however (see Addendum). The same intermediate carbene was postulated for the aqueous-phase irradiations. Under these conditions, a longer lifetime is required of the hydroxycarbene in order to allow dimerization to acetoin.



(64)

All of the reactions of pyruvic acid are considered to originate from the triplet state[62,63]. An intense phosphorescence was observed in ethanol glass (77 K) with a 0–0 band at 423 nm (68 kcal) for **107** and 470.5 nm (60.8 kcal) for **108**, ensuring efficient intersystem crossing. In spite of this, the gas-phase photoreactions could not be quenched by oxygen, suggesting a very short-lived excited state.

In addition to these studies on pyruvic acid, a few other examples of photodecarboxylation of α-keto acids have recently appeared. Davidson[90] and Jefford and coworkers[104] have reported that photosensitization of α-keto carboxylic acids leads to decarboxylation although different mechanistic pathways are proposed by each group of authors (equation 65). The sensitizers employed were methylene blue



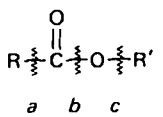
(65)

(a) R = *t*-Bu (95%)
(b) R = *n*-Pr (40%)
(c) R = $(CH_2)_2CO_2H$ (45%)

and Rose Bengal, low triplet energy sensitizers used primarily for generating singlet oxygen. Jefford found that the reaction proceeds only in the presence of added O_2 while Davidson found that the photodecarboxylation occurred most readily in the absence of oxygen, as long as the sensitizer is not bleached by the reaction products. Energy transfer from the lower energy triplet of the dye to the α-keto acid would be unfavourable but is the mechanism favoured by Davidson for the anaerobic reaction. At present, the mechanism for this reaction must be considered as unresolved (see Addendum, however).

B. Esters and Lactones

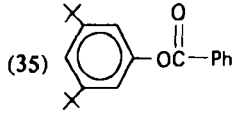
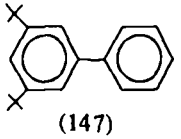
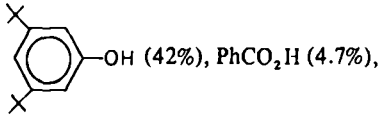
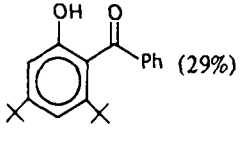
Just as with the carboxylic acids, esters and lactones photochemically extrude carbon dioxide (Table 8). The aliphatic derivatives such as methyl acetate (**141**), methyl propionate (**143**) and the alkyl formates (**139**) yield a variety of products resulting from the initial homolytic cleavage of one of the three bonds to the carboxyl group[105–113]. Though mechanistically intriguing, these reactions have



limited synthetic usefulness because of the large number of products. At least one synthetic application has appeared, however. Irradiation of 3β-acetoxy-5α-cholestane (**167**) in mixtures of hexamethylphosphoric triamide (HMPA)*–H_2O

*Caution should be exercised in the use of HMPA.

TABLE 8. Photodecarboxylation of esters and lactones

Ester (Lactone)	Conditions[a]	Products (yields)	Reference
(139) Methyl formate (alkyl formates)	Hg arc, vapour, quartz, liquid (see text)	CO_2 (15%), CO (40%), CH_3OH (29%), H_2(10%), (Φ_d = 0.75)	105, 108, 110
(140) Methyl carbonate	Hg, mp, quartz, gas phase	CO_2, CO, CH_4, C_2H_6, CH_3OH	105a
(141) Methyl acetate	Hg, mp, quartz, vapour	CO_2, CO(major), C_2H_6, CH_4	107, 108, 109, 112
(142) Propiolactone	254 nm, neat liquid	CO_2(0.007%), CO (0.005%), C_2H_4 (0.001%), CH_3CHO	106
(143) Methyl propionate	Hg, mp, neat liquid	CO_2, CO, C_2H_6, CH_4, C_2H_4, C_3H_8	108, 111, 113, 114, 115
(144) Methyl butyrate	Hg, mp, neat liquid	CO_2, CO, C_2H_4, C_3H_8, CH_4, C_3H_6	108, 61
$ArCH_2OCOCH_3$	Hg, hp, 275 nm filter, dioxane–H_2O	CO_2, $ArCH_2CH_2Ar$, $ArCH_2OH$, others (see text)	15
(4) (*p*-anisyl = Ar)			
(9) (*m*-anisyl = Ar)			
(11) (3,5-dimethoxyphenyl = Ar)			129
(145) $Ar_2CHOCOCH_3$	Hg, hp, 275 nm filter, dioxane–H_2O	CO_2, Ar_2CH_2, Ar_2CHOH (see text)	15
(146) Ethyl acetate	215–235 nm, quartz, gas, liquid, solid phase	CO_2, CO, C_2H_4	116
(35) 	Hg, mp, quartz, benzene	CO_2,  (14%), (147)  (42%), $PhCO_2H$ (4.7%), **35** (35%),  (29%)	26

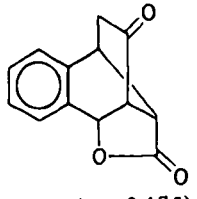
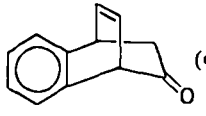
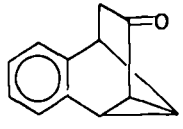
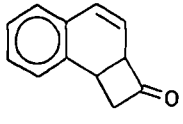
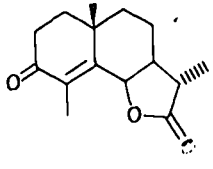
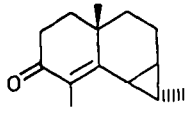
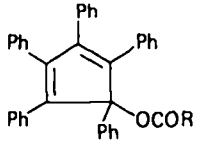
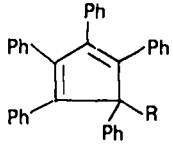
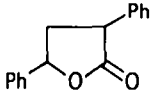
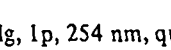
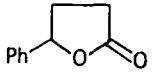
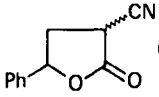
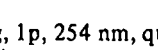
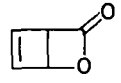
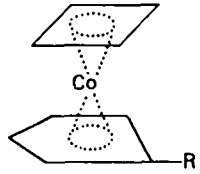
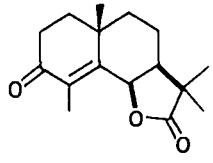
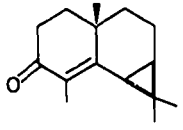
(148)  (Φ_d, 0.175)	Hg, mp, 300 nm, quartz, benzene	CO_2 (Φ, 0.148), naphthalene (Φ, 0.046), ketene,  (Φ, 0.029),  (Φ, 0.061),  (Φ, 0.001)	117, 120, 124, 145
(149) 	Diffuse light, Pyrex, benzene		118
(150) 	Hg, hp, benzene	CO_2 (81%)  [R = CH_3 (81%) R = C_2H_5 (80%)]	119

TABLE 8. (Continued)

Ester (Lactone)	Conditions[a]	Products (yields)	Reference
(151)  (a) *cis* (Φ_{dis}, 0.045) (b) *trans* (Φ_{dis}, 0.051)	Hg, 1p, 254 nm, quartz, dioxane	CO_2,  (*cis* and *trans*) [from **151a**: Φ = 0.026 (51%); from **151b**: Φ = 0.027 (51%)]	120, 124
(152)  (Φ_{dis}, 0.026)	Hg, 1p, 254 nm, quartz, dioxane	CO_2 (Φ, 0.02), phenylcyclopropane	120, 124
(153)  (Φ_{dis}, 0.092)	Hg, 1p, 254 nm, quartz, dioxane	CO_2 (Φ, 0.1),  (*cis* and *trans*) (77%)	120, 124
(154) $Ar^1CH_2CO_2CH_2Ar^2$ (a) Ar^1, Ar^2 = Ph (b) Ar^1, Ar^2 = *p*-anisyl (c) Ar^1, Ar^2 = *p*-tolyl (d) Ar^1, = *p*-tolyl, Ar^2 = *p*-anisyl (e) Ar^1 = *m*-anisyl, Ar^2 = *m*-tolyl (f) Ar^1 = *m*-tolyl, Ar^2 = *m*-anisyl (g) Ar^1 = Ph, Ar^2 = 2-furyl	Hg, 1p, 254, quartz, dioxane	CO_2, $Ar^1CH_2CH_2Ar^2$, $Ar^1CH_2CH_2Ar^1$, $Ar^2CH_2CH_2Ar^2$ (for yields, etc., see text)	120, 124, 130, 132, 135
(155) Methyl phenylacetate (Φ_{dis}, 0.099)	Hg, mp, Vycor, methanol 31°C	CO_2 (Φ, 0.020), CO (Φ, 0.028), CH_4 (Φ, 0.009), bibenzyl (Φ, 0.02), 2-phenylethanol (Φ, 0.01)	75
(156) 	Hg, mp, Corex, ether and substituted cyclopentadienylcobalt dicarbonyl as the cyclobutadiene trapping agent	 [R = H (17%) R = CO_2Me (26%)]	121
(157) 	Diffuse sunlight, Pyrex, solid	CO_2,  (85%)	122

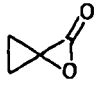
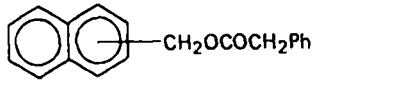
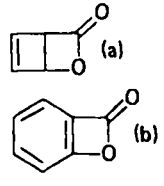
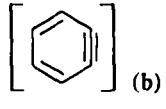
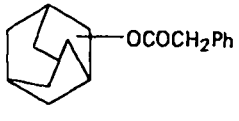
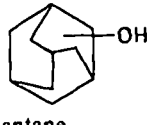
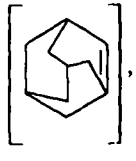
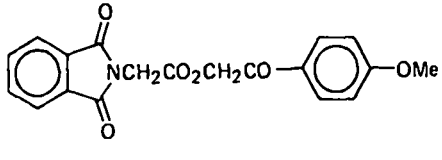
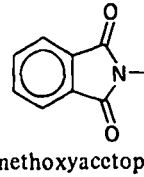
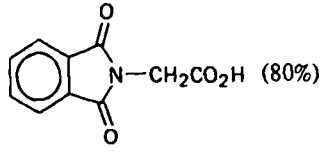
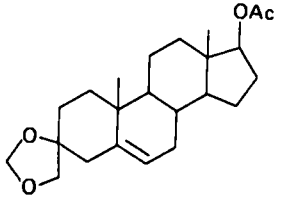
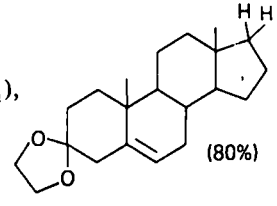
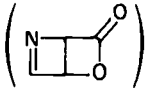
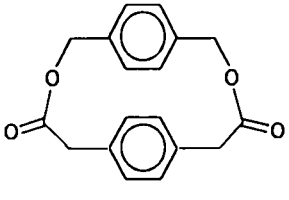
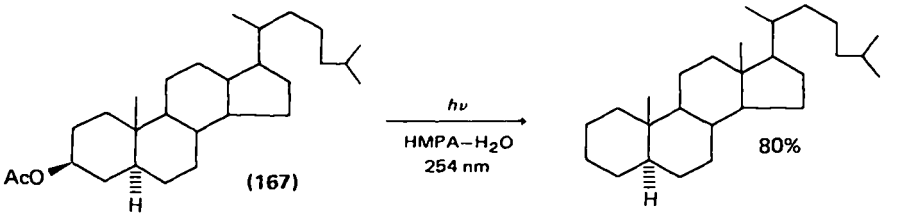
(158)		Hg, hp, quartz, neat, 77 K	CO_2, allene	29
(159)	$R{-}CO_2CHPh_2$ $R = CH_3, C_2H_5, C_3H_7$, *cyclo*-C_6H_{11}, $PhCH_2$	Hg, hp, quartz, benzene	CO_2, $RCHPh_2$ (50–70%), CH_2Ph_2 (7–10%), $Ph_2CHCHPh_2$ (10–20%)	123
(160)		254 nm, quartz, dioxane, benzene	CO_2 (see text), $C_{10}H_7{-}CH_2CH_2Ph$, $PhCH_2CH_2Ph$, $C_{10}H_7{-}CH_2CH_2C_{10}H_7$	120, 124, 128, 130, 132, 135
(161)		Hg, quartz, argon matrix, 8 K	CO_2,  (a)  (b)	125, 37
(162)		254 nm, quartz, methanol	CO_2,  ,  , adamantane	126
(163)		Hg, mp, quartz, dioxane	CO_2  (?), *p*-methoxyacetophenone,  (80%)	127

TABLE 8. (Continued)

Ester (Lactone)	Conditions[a]	Products (yields)	Reference
(164) $PhCH(CH_3)OCOCH_2Ph$	Hg, lp, 254 nm, quartz, dioxane	CO_2, not identified	130, 135
(165) 	254 nm, quartz, HMPA–H_2O	(CO_2),  (80%) (additional examples, see text)	131
(166) 	Hg, Pyrex, argon matrix	CO_2, HCN, C_2H_2	133
(167) 	254 nm, quartz, DME (dimethoxyethane)	CO_2, paracyclophane (~70%)	134

[a] See table 3 for format.

(95:5) at 254 nm gave cholestane in 80% yield[131] (equation 66). Whether this

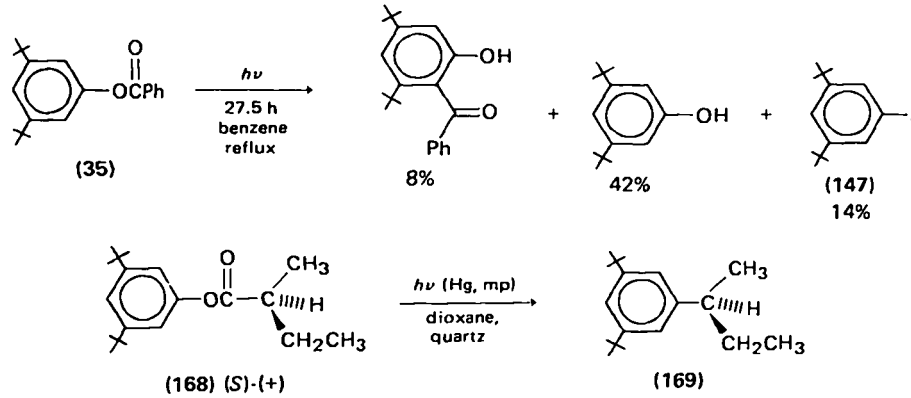


(66)

reaction actually involves a photodecarboxylation is questionable as no evidence for CO_2 production was given. A number of other acetates and formates were also examined but again no attempt was made to determine the fate of the acid moiety[131]. Nevertheless, this reaction does afford a useful route for the reductive displacement of acetoxy groups.

Another simple carboxylic acid derivative which does not give a complex product mixture on irradiation is methyl carbonate (**140**). Wijnen[114] determined the rate of CO_2 production to be more than five times the rate of CO formation and showed that the only major products from the reaction were methane and methanol plus a smaller amount of ethane.

For aryl esters, photodecarboxylation is often only a minor side reaction, especially for several of the aryl esters which undergo the photo-Fries rearrangement[26]. The irradiation of 3,5-di-*t*-butylphenyl benzoate (**35**) gave the photo-Fries product (8%), 3,5-di-*t*-butylphenol (42%) from decarbonylation, and a 14% yield of biphenyl (**147**) from decarboxylation (equation 67). A few other examples of the

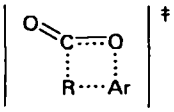


(67)

(68)

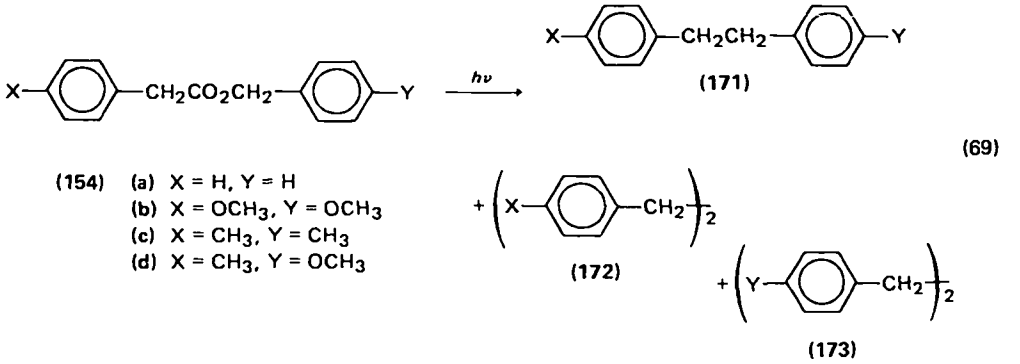
formation of decarboxylation by-products for the photo-Fries rearrangement have also been reported[20,26,137], principally from hindered aryl benzoates. Esters examined by Knutson[26,138] and by Bradshaw[137] photodecarboxylate most efficiently in ether, dioxane or benzene at the expense of photo-Fries product formation. In ethanol, however, the rearrangement occurred with little or no photodecarboxylation.

An intriguing stereochemical probe was employed by Knutson[138] in order to examine the fate of an alkyl group during the photodecarboxylation process. Thus, photodecarboxylation of 3,5-di-*t*-butylphenyl (*S*)-(+)-2-methylbutanoate (**168**) gave **169** with retention of configuration at the asymmetric carbon (equation 68). This contrasted with the decarbonylation process to **170** where complete racemization occurred. The rearrangement step suggested by the authors was a concerted process via a four-centre transition state:



A similar photodecarboxylation has been suggested as a process accompanying the photosolvolysis of substituted benzyl acetates. Irradiation of 4-methoxybenzyl acetate (**4**) in dioxane gave a solvent-derived coupling product (**7**), as well as di-*p,p'*-dimethoxydibenzyl (**5**)[15] [See Section II.E, equations (12–14)]. The analogous products were also observed, albeit as minor products, from irradiation of 3-methoxybenzyl acetate (**9**), but were completely absent from the product mixture from irradiation of 3,5-dimethoxybenzyl acetate (**11**)[15]. The major products in these latter two studies were the alcohols formed by a photosolvolysis reaction.

In general, however, arylmethyl esters have proved to be a rich source of photodecarboxylation reactions. Two independent studies[75c,120,124] of benzyl phenylacetate (**154a**) have shown that photodecarboxylation provided a 90% yield of bibenzyl (**171a**, equation 69). Likewise, the di-*p,p'*-anisyl and di-*p,p'*-tolyl



(69)

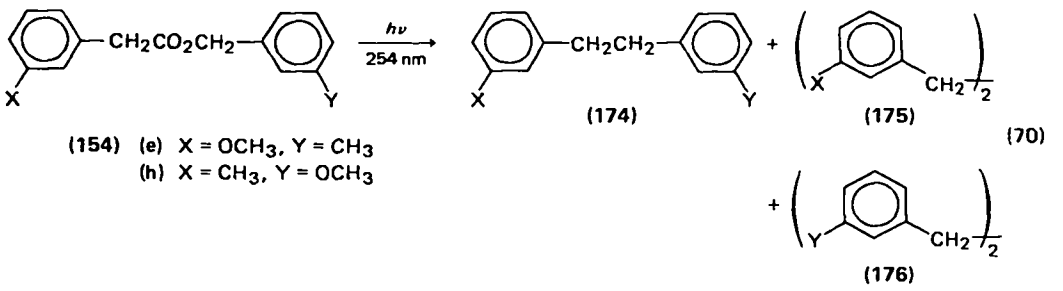
(154) (a) X = H, Y = H
(b) X = OCH_3, Y = OCH_3
(c) X = CH_3, Y = CH_3
(d) X = CH_3, Y = OCH_3

(171)

(172)

(173)

derivatives (**154b** and c) gave the corresponding dibenzyls in good yield. The 'mixed' ester **154d** gave three dibenzyl products, **171**, **172** and **173**, in a ratio of 2.5:1:1, an indication that the product-forming step involves coupling of the substituted benzyl radicals generated upon decarboxylation. The *meta* isomers (equation 70) followed the same course, an indication of the lack of substituent effects on the nature of the reaction[117,124]. These results are in marked contrast

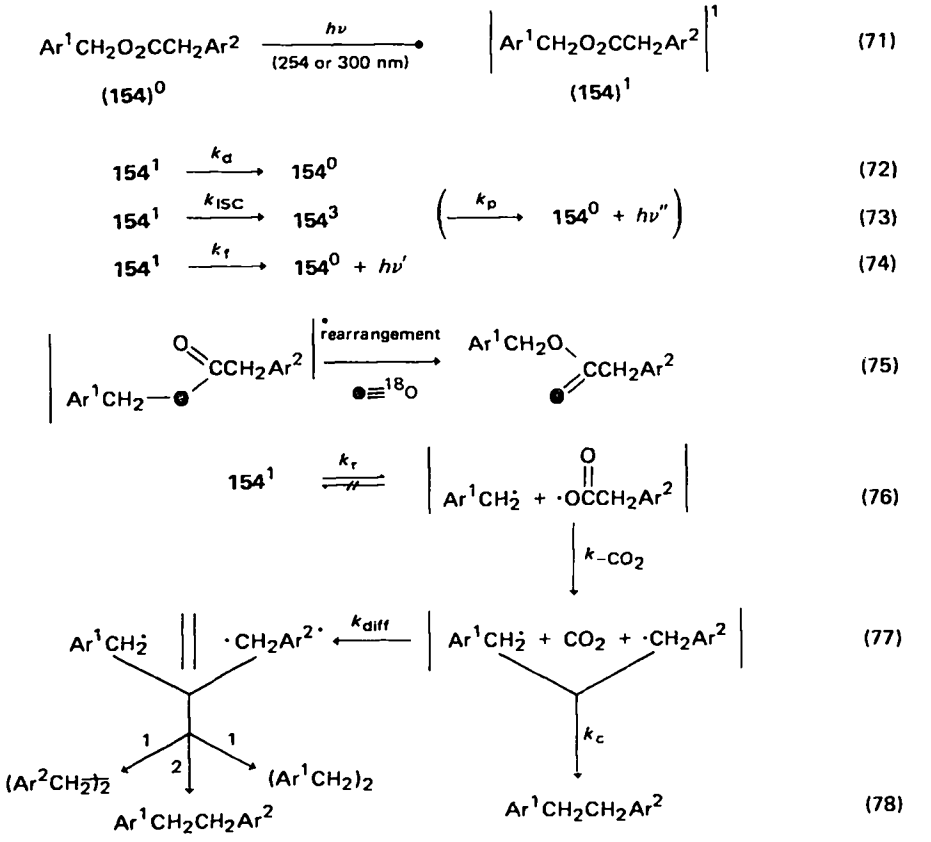


(154) (e) X = OCH_3, Y = CH_3
(h) X = CH_3, Y = OCH_3

(70)

with the behaviour of the benzyl acetates examined by Zimmerman and Sandel[7,15], and discussed earlier. Accordingly, attempts to force the ionic reaction by irradiations in aqueous dioxane (20% v/v) and methanol saturated with sodium acetate (~1.4 M) were unsuccessful[124].

As shown in Table 9, the yields of hydrocarbon products from photodecarboxylation reactions vary from 50 to 95%. However, the synthetic potential of photodecarboxylation and the photoreaction's efficiency are limited for the following



SCHEME 7. General mechanism of arylmethyl ester photodecarboxylations.

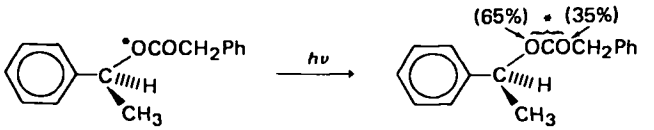
TABLE 9. Photodecarboxylation yields of arylmethyl arylacetates

	Ester $Ar^1CH_2O_2CCH_2Ar^2$	Solvent[a]	Φ_d	Φ_{CO_2}	% Yield(ϕ) $(Ar^1CH_2)_2$	$Ar^1CH_2CH_2Ar^2$	$(Ar^2CH_2)_2$
(154)	(a) Benzyl phenylacetate	D[b]	0.033	0.03	–	57 (0.023)	–
		M[c]	0.19	–	–	91	–
	(b) *p*-Methoxybenzyl *p*-methoxyphenylacetate	D[b]	0.25	0.19	–	84	–
	(c) *p*-Methylbenzyl *p*-methylphenylacetate	D[b]	0.25	–	–	88 (0.22)	–
		M[c]	0.25	–	–	93	–
	(d) *p*-Methylbenzyl *p*-methoxyphenylacetate	D[b]	–	–	22	56	22
	(e) *m*-Methylbenzyl *m*-methoxyphenylacetate	D[b]	0.075	–	16 (0.012)	59 (0.044)	16 (0.012)
	(f) *m*-Methoxybenzyl *m*-methylphenylacetate	D[b]	0.23	–	12 (0.028)	83 (0.19)	14 (0.032)
	(h) Benzyl *p*-methylphenylacetate	M[c]	0.13	–	16	45	14
	(i) *p*-methylbenzyl *p*-methylphenylacetate	D[b]	0.28	–	20	48	20
(160)	(a) 1-Naphthylmethyl phenylacetate	D[b,d,e],B	0.0057	–	1	11[f](0.0008)	1
	(b) 2-Naphthylmethyl phenylacetate	D[d,e],B	0.055	–	1	11[f](0.015)	1
	(c) 2-Naphylmethyl 2-naphthylacetate	B[d]	–	–	–	80 (0.010)	–
	(d) Phenyl 2-naphthylacetate	B[d]	<0.0001	–	*g*	*g*	*g*
	(e) Phenyl 1-naphthylacetate	B[d]	<0.0001	–	*g*	*g*	*g*

[a]The solvents employed (and the irradiation wavelength) were: D = dioxane (254 nm), M = methanol (254 nm), B = benzene (300 nm).
[b]References 120 and 124.
[c]Reference 75c.
[d]Reference 128.
[e]300 nm irradiations.
[f]Ratio of products by vpc.
[g]Not determined quantitatively; very little product formed.

reasons: (*i*) Radical coupling processes can lead to a complicated mixture of products (entries **154a, d, e, f, i,** and **160a, b**); (*ii*) the absorbing chromophore must be the arylmethyl alcohol moiety (entries **154b, c, i** vs **h**, **154f** vs **e**, **160a** vs **e** and **160b** vs **d**); (*iii*) cage effects can dominate (entries **160a, b**).

A general mechanistic scheme has been developed for this reaction and is outlined in Scheme 7[128,135]. The individual steps were established from isotopic labelling results, spectroscopic studies and stereochemical probes with a wide variety of esters. After initial excitation of the ester, the excited singlet either reacts to eventually yield products ($\Phi < 0.3$) or emits a fluorescence characteristic of the aromatic chromophore (equations 71, 76 and 74, respectively). Low-temperature phosphorescence studies have shown that the esters intersystem cross to the triplet and emit phosphorescence also typical of the aromatic chromophore (equation 73). In competition with the usual excited singlet-state processes of fluorescence, intersystem crossing, and homolytic cleavage is a hidden rearrangement in which the two carboxyl oxygens are interchanged (equation 75). This was discovered by ^{18}O-labelling studies with esters **154a** (Φ_{re}, 0.02) (re = rearrangement), **160a** (Φ_{re}, 0.04) and **160b** (Φ_{re}, 0.16) and for α-methylbenzyl phenylacetate (**164**). Ironically, the oxygen interchange reaction is more efficient than the photodecarboxylation process[130,135]. Thus, the ^{18}O studies revealed a significant energy wastage process for this reaction[94].



(79)

[(*S*)-(−)-**164**] [(*S*)-(−)-**164**]
$[\alpha_D]$ −55° $[\alpha_D]$ −54.9°

The nature of this process was studied employing (*S*)-(−)-α-methylbenzyl phenylacetate [(*S*)-(−)-**164**], which was not racemized during irradiation even at 52% conversion to products and concomitant 35% ^{18}O-interchange of the carboxyl oxygen atoms (equation 79)[130,135]. This result, and additional studies with lactones (*vide infra*), have led to the suggestion that the interchange reaction is a 1,3-suprafacial benzyl migration with retention of configuration of the migration carbon, i.e. a photochemically allowed $\pi^2s + \sigma^2s$ migration[139].

The homolytic cleavage process, which eventually leads to decarboxylation, generates a pair of radicals as shown in equation (76). Although the rate constant for this process was not measured directly, relative values for the cleavage step were obtained for the naphthylmethyl esters **160a, b, d** and **e**. This was possible because the reaction was shown to occur exclusively from the singlet state of the ester for this series, and the naphthyl esters emitted a strong fluorescence which was useful for obtaining the lifetime (τ) of the reactive excited state. As outlined in Section II, the lifetime and the quantum efficiency are directly related to the rate constants for a unimolecular process from a specific excited state (by equations 2, 5, 6 and 8, for singlet states). These equations when combined, yield equation (80), which

$$\frac{k_r}{k_r'} = \left(\frac{\Phi_r}{\Phi_r'}\right)\left(\frac{\Phi_f'}{\Phi_f}\right)\left(\frac{\tau_0'}{\tau_0}\right) \tag{80}$$

relates the rate constants for two different esters to the efficiencies for reaction and fluorescence and to the natural singlet lifetime. Values for Φ_f and τ_0 for each ester

TABLE 10. Fluorescence quantum yields and relative rates for singlet processes of α- and β-naphthyl esters[a]

Ester	$10^{-3}\Phi$[b]	k_r(rel.)[c]	Φ_f(rel.)[c,d]	$10^{-9}\tau_0$(s)[e]	$10^{-9}\tau_s$(s)[f]
(160) (a)	5.7	0.11 ± 0.02	1.08 ± 0.25	7.2 ± 1.0	8.0 ± 0.6[g]
(b)	55.0	1.00	1.00	7.1 ± 1.0	8.0 ± 0.8
(d)	<0.1	$<(1.8 \pm 0.5) \times 10^{-3}$	0.88 ± 0.18	8.1 ± 1.0	10.8 ± 0.8
(e)	<0.1	$<(1.6 \pm 0.2) \times 10^{-3}$	1.10 ± 0.12	8.7 ± 1.0	8.2 ± 0.7

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[b]Direct irradiations in benzene or dioxane at 300 nm. Quantum yields were determined using a potassium ferrioxalate actinometer in the apparatus described in Reference 124 by extrapolating the results of several runs to 0% conversion (Table 9).
[c]Related values based on ester **160b**.
[d]Determined from peak heights of the fluorescence emission for the four esters in cyclohexane and dioxane.
[e]Values obtained by integration of the u.v. band in dioxane and cyclohexane[140].
[f]Values obtained by oxygen quenching of the fluorescence in cyclohexane[10].
[g]This was shown to be 17 ns by single photon counting techniques. (Reference 128).

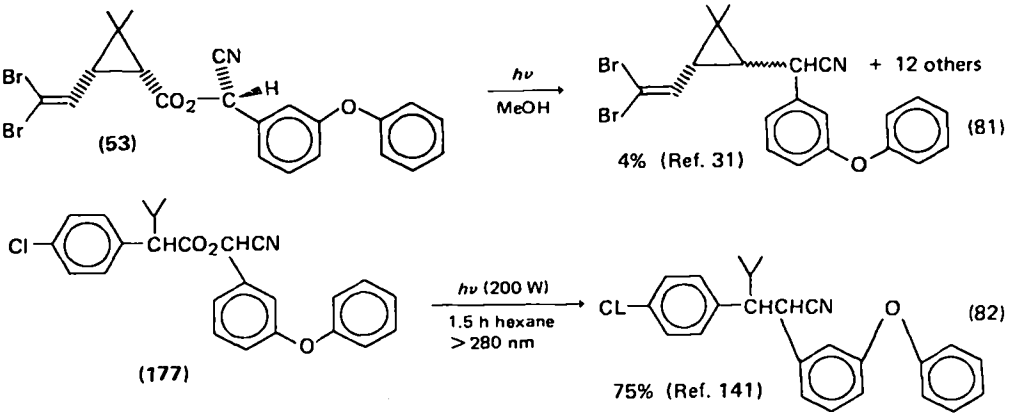
were employed to obtain relative k_r values for the esters **160a, b, d, e** (Table 10). As shown in column 2, the relative rates for homolytic cleavage are strongly position dependent. The rate constants of the α- and β-naphthylmethyl esters (**160a** and **b**) differ by an order of magnitude, with the β-isomer being the more reactive. This result is unusual in that it is the reverse of the expected thermodynamic order of reactivity, indicating the dominance of other important factors. This is another example of an increasingly common observation of the reversal of ground-state substituent effects, in electronic excited-state chemistry. For the naphthylmethyl ester singlet state, a dominating factor may be the direction of the transition dipole[128]. Finally, the naphthylacetates **160c, d** were essentially unreactive, in accord with earlier observations for the substituted benzyl esters[75c].

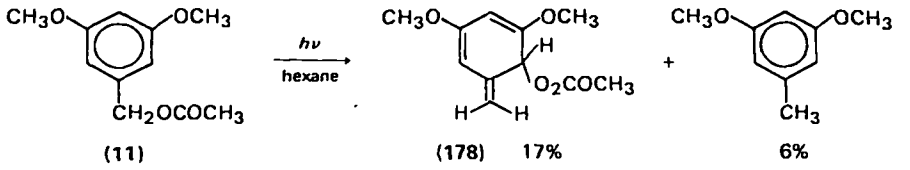
Once the pair of radicals are generated, a rapid loss of CO_2 is expected as shown in equation (76) (Scheme 7). Then the arylmethyl radicals undergo typical coupling or abstraction reactions which are largely controlled by normal free-radical processes. For example, the importance of solvent parameters is illustrated by comparison of the product ratios from the naphthylmethyl and benzyl esters (Table 9). For the larger, less mobile naphthylmethyl radicals, cage combination dominates yielding principally $Ar^1CH_2CH_2Ar^2$ (equation 78, $k_c > k_{diff}$). For the more mobile benzyl radical derivatives, diffusion from the solvent cage dominates ($k_{diff} \gg k_c$) and a nearly statistical ratio of hydrocarbons is formed.

Solvent viscosity also influences the product ratio. For example, the product ratio from *p*-methylbenzyl *p*-methoxyphenylacetate (**154d**) displays a pronounced solvent dependence. The cage combination process (k_c, to yield **171b**) is dominant in alcohol solvents and less important in less viscous hydrocarbon solvents. If irradiations of **160b** are performed at −77°C in benzene (as a glass) the ratio of the three coupling products is 1:30:1, showing a significant increase in the cage combination process[130,135].

Finally, direct evidence for benzyl radical formation has been provided by the elegant work of Meiggs, Grossweiner and Miller[75b,c]. The absorption spectrum ($\lambda_{max} = 314$, $a = 1500\ M^{-1}\ cm^{-1}$) and combination rate constants ($1.36 \times 10^9\ M^{-1}\ s^{-1}$ at 25°C were determined by flash photolysis of benzyl phenylacetate (**154a**).

Other studies on benzyl and arylmethyl esters have subsequently confirmed the generality of the mechanism depicted in Scheme 6. Some notable examples are benzhydryl esters (**159**)[123], 1-adamantyl phenylacetate (**162**)[126], several pyrethroid esters (e.g. **53**[31] and **177**[141], equations 81 and 82), 3,5-dimethoxybenzyl acetate (**11**, equations 14 and 83)[15,129,132] and benzyl acetate (**179**,





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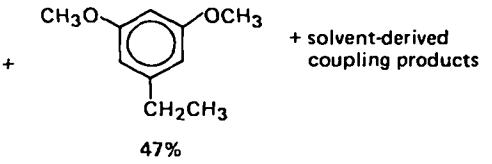

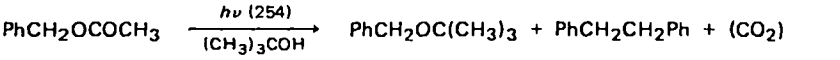

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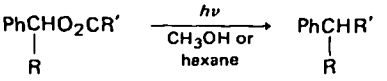


(85)

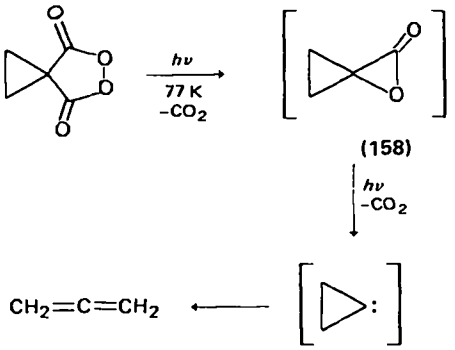
R = H, CN or C_2H
R' = CH_3, n-C_3H_7, c-C_3H_5, $CH_2C(CH_3)_3$ or CH_2Ph

equation 84)[142], several α-substituted benzyl esters (equation 85)[141], cyclopentadienyl esters (**150**)[119] and 2-furfuryl phenylacetate (**154g**)[124].

In general the decarboxylation yields are high for this structurally diverse group of esters. Of the examples cited, one merits additional attention. The work of Jaeger[129,132] has revealed that the photochemisty of the 3,5-dimethoxybenzyl acetates (equation 83) is more complex than the one-step photosolvolysis depicted earlier by Zimmerman[15]. In fact, rearrangement to **178** represents a substantial proportion of the reaction, and can also be considered an 'energy-wasting' step in that the product would most likely revert to the ester **11** or fragment to the products observed. Oxygen-18 studies with ester **11** showed extensive oxygen interchange[132], in accord with the results found for **154a**, **160a**, **b** and **164**.

This photodecarboxylation mechanism can be extended to a number of lactones. The decarboxylation of lactones often leads to the formation of a smaller (n − 2) ring, as well as to internal disproportionation products. The variety of examples of lactone photodecarboxylations is very extensive, as illustrated by the reactions of lactones **142**, **148**, **149**, **151**–**153**, **156**–**158**, **161**, **166** and **167** (Table 8) and **14**, **47** and **48** (Table 3). As with the esters, the lactones can be divided into aliphatic and arylmethylene compounds. This grouping enables one to predict the reactivity and types of products expected upon irradiation.

The aliphatic derivatives include α-, β- and γ-lactones. The only example of an α-lactone decarboxylation is the highly strained spirocyclopropyl α-lactone **158** (equation 86). Chapman and coworkers[29] observed the α-lactone formation by infrared measurements in argon matrices. The major products of the irradiations were allene and CO_2, which probably arose from irradiation of the lactone. As noted earlier (Section III), other α-lactone derivatives undergo photo-



(86)

decarbonylation to the corresponding ketones. The added strain of a cyclopropane ring in **158** must influence the initial bond-cleavage step.

For β-lactones, decarboxylation is a major pathway. Propiolactone (**142**), the subject of a very early photochemical study by Linnell and Noyes[106], photodecarboxylated to ethylene ($\Phi = 10^{-3}$). The major competing process was decarbonylation. This reaction has been extensively exploited by Chapman[125a–c], by Shirk[125f], by Krantz[125g,h] and by Rosenblum[121] as a route to cyclobutadiene (**180**, equation 87). In Chapman's study, photolysis of 2-oxabicyclo[2.2.0]hex-5-en-3-one (**156**, the photoproduct of α-pyrone, **181**[143]), at 8 K in an argon matrix with unfiltered u.v. light, yields cyclobutadiene, which was identified by its infrared spectrum (Figures 8 and 9). The bands for carbon dioxide and those

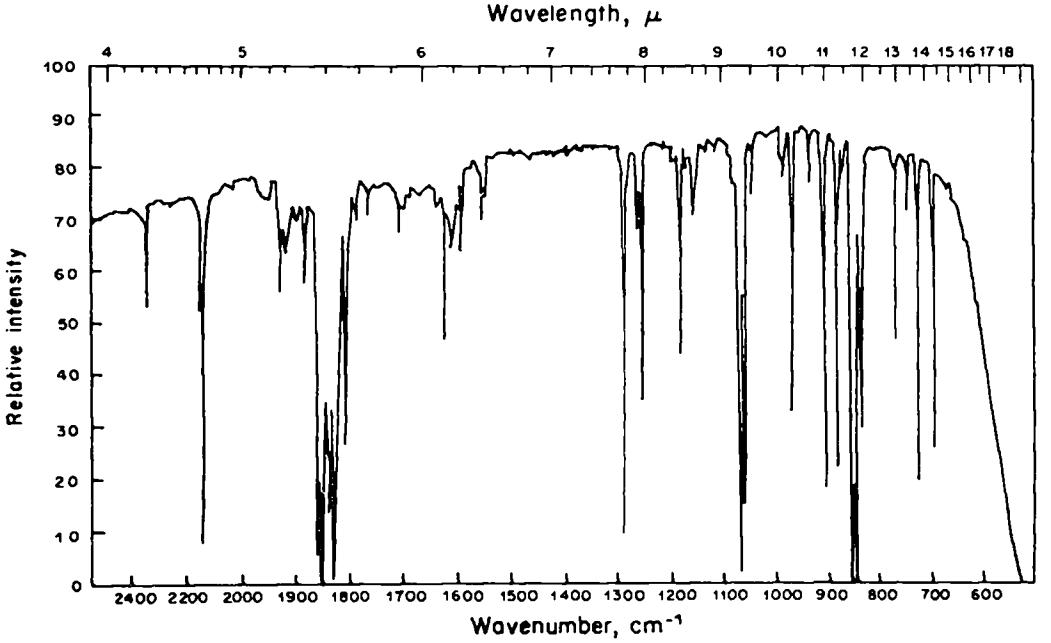


FIGURE 8. Photo-α-pyrone (181) matrix isolated in argon, prepared by 11.5 h irradiation (> 2910 A) of α-pyrone at 8 K. Reprinted with permission from O. L. Chapman, C. L. McIntosh and J. Pacansky, *J. Amer. Chem. Soc.*, 95, 614 (1973). Copyright by the American Chemical Society.

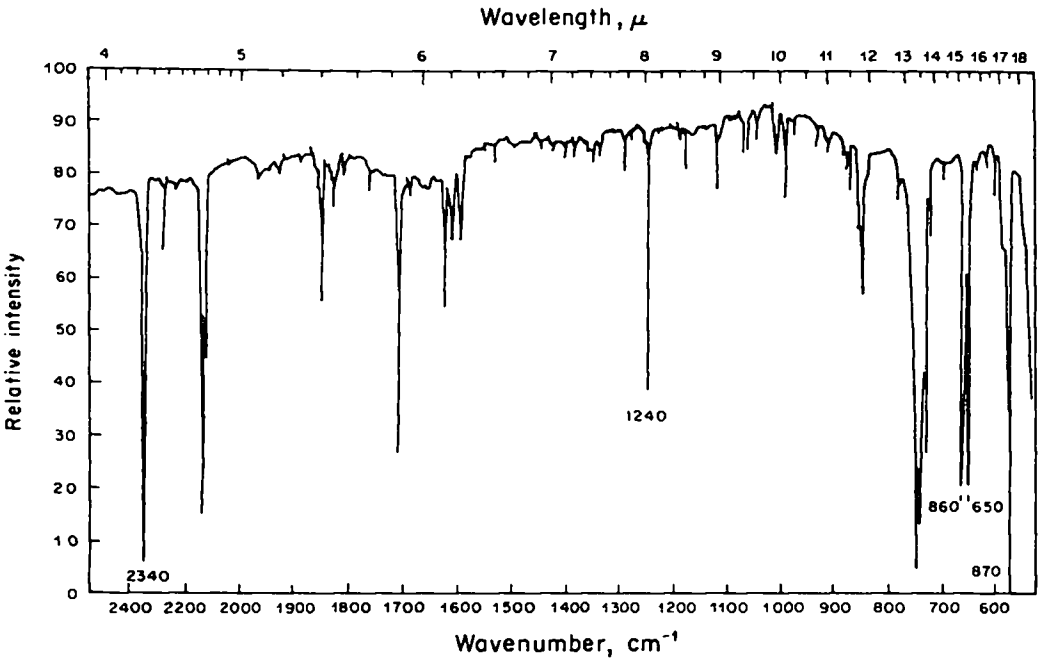
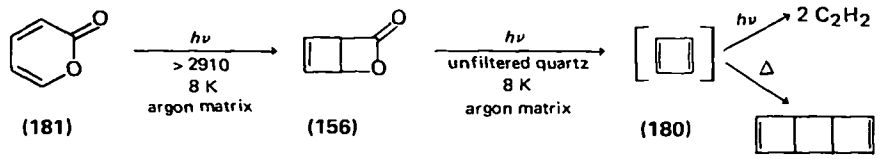


FIGURE 9. Sample shown in Figure 8 after 267 min irradiation through quartz at 8 K. The new bands in the 745 cm^{-1} region ot the spectrum are due to the photoproduct of cyclobutadiene. Reprinted with permission from O. L. Chapman, C. L. McIntosh and J. Pacansky, *J. Amer. Chem. Soc.*, 95, 614 (1973). Copyright by the American Chemical Society.

attributed to cyclobutadiene were followed over a period of three hours. Plots of the intensities vs time are shown in Figure 10. The infrared spectrum of **180** was



consistent with that expected for a square planar (D_{4h}) structure. Additional evidence in favour of this intermediate and its symmetry was derived from a series of deuterium-labelling studies. The same labelled 1,3-dideuteriocyclobutadiene was generated from both 3,5- and 4,6-dideuterio-α-pyrone (equation 88). Furthermore, 1,3-dideuteriocyclobutadiene photolysed to a single monodeuterioacetylene. Complementary results were obtained with 3,6- and 5,6-dideuteriopyrones, which gave a 1,2-dideuteriocyclobutadiene. These results also rule out the intermediacy of the elusive tetrahedrane structure, which would have been common to all four dideuterio-α-pyrones and would have given three isotopic acetylenes[125b]. In contrast to the photodecomposition of cyclobutadiene to acetylene, the thermal reaction of **180** is cycloaddition to tricyclo[4.2.0.$0^{2,5}$]octa-2,7-diene (equation 87).

Cyclobutadiene can be trapped as either the iron tricarbonyl complex or the cyclopentadienylcobalt complex when α-pyrone is irradiated in the presence of the corresponding metal carbonyl reagent[121]. The yields are from 5 to 17% based on

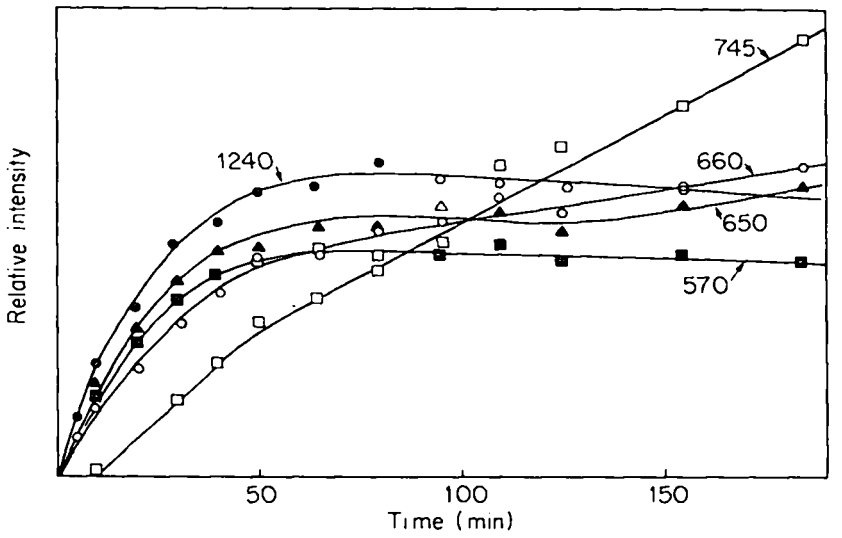
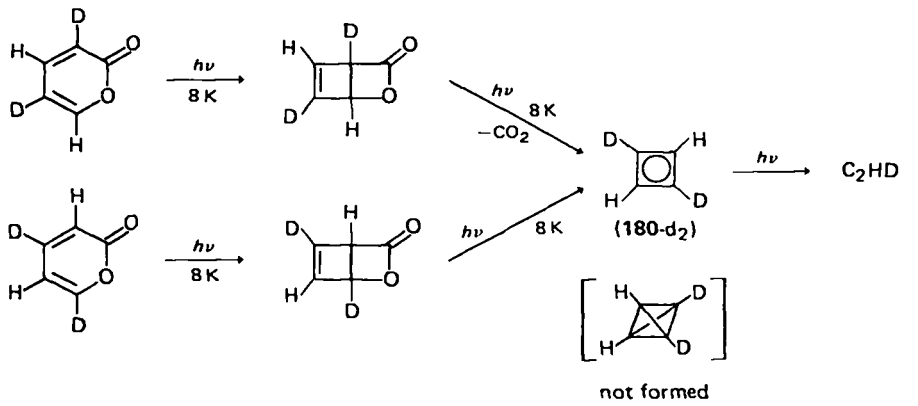


FIGURE 10. Plot of relative intensity of significant bands as a function of irradiation time. Cyclobutadiene bands are 1240 (•), 650 (▲) and 570 (■) cm^{-1}. The carbon dioxide bending mode is 660 cm^{-1} (○). The most intense band in the cyclobutadiene photoproduct is 745 cm^{-1} (□). Reprinted with permission from O. L. Chapman, C. L. McIntosh and J. Pacansky, *J. Amer. Chem. Soc.*, 95, 614 (1973). Copyright by the American Chemical Society.



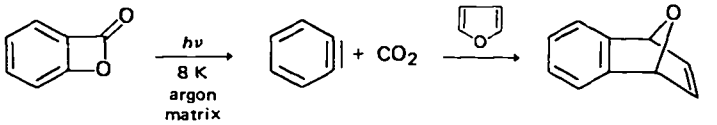
(88)

the metal carbonyl. This represents a potential synthetic entry to cyclobutadiene which has not been extensively exploited.

Attempted synthesis of azacyclobutadiene by the electrocyclization of 5-aza-α-pyrone to **166** followed by photodecarboxylation gave only HCN and C_2H_2. The azacyclobutadiene was suggested as an intermediate[133].

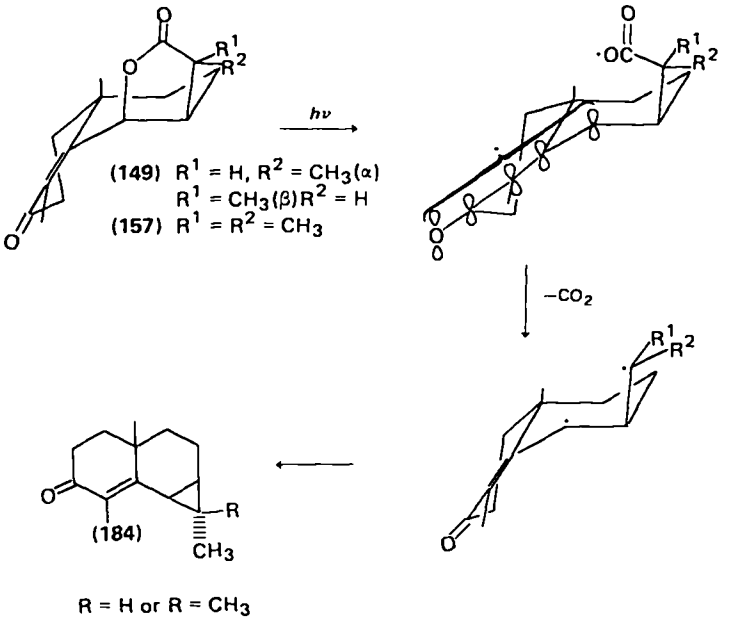
Another reactive intermediate of intense theoretical interest is benzyne (**182**). Chapman[144] has also generated this species in an argon matrix at 8 K by irradiation of phthaloyl peroxide. The initial product is benzpropiolactone (**161**) which subsequently loses a second molecule of CO_2 to give benzyne. As before, the structure of this intermediate was established by its infrared spectrum

(1627, 1607, 1451, 1053, 1038, 849, 736 and 469 cm^{-1}) and also by trapping experiments with furan (equation 89).



(161) (182) (89)

The five-membered ring lactones represent the most extensively explored group within this functionality. Early studies on aliphatic γ-butyrolactones illustrated the multiplicity of photodecomposition pathways for lactones in particular and esters in general. Simonaitis and Pitts[16,17] showed that α-, β- and γ-cleavage reactions occur with unsubstituted and α- or γ-methyl-γ-butyrolactones (**14**, **47** and **48**), as discussed earlier (see Section III.A). In contrast to these studies, a number of more recent studies have shown that for certain substituted γ-butyrolactones decarboxylation dominates the photochemical decomposition modes. Most notable are the studies by Perold and Ourisson[118] on the dihydrosantonines. Irradiation of either the α- or β-methyl (**149**)[118,122] or dimethyl (**157**)[122] derivative gave a single product, **184** (equation 90).

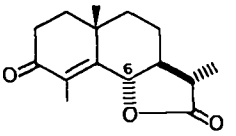


(90)

Three features of these transformations which are indicative of the mechanism for most of the known examples of photodecarboxylation of substituted γ-butyrolactones are: (*i*) The ether oxygen of the lactone must be allylic to the excited chromophore. (*ii*) Orbital alignment of the same γ-C–O sigma bond must be parallel with the π orbitals of the chromophore for maximum efficiency – a stereoelectronic requirement. (*iii*) The extrusion is generally not stereospecific.

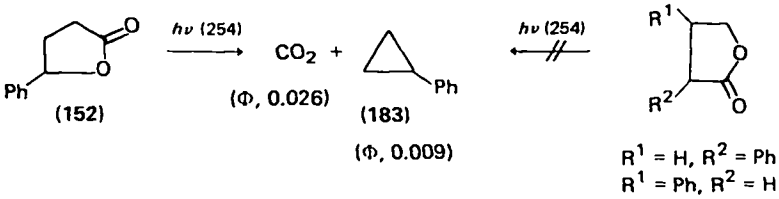
Although all of these features have not been firmly established in most cases, for a large number of examples the relationship of reactant and product structures is consistent with the three requirements. The orbital alignment requirement is well

illustrated by Perold and Ourisson's study[118] of the C_6 epimer of **149** which is photochemically inert[122]. Several other examples included below are also illustrative of this stereoelectronic requirement.



(149)

The photodecarboxylation process occurs most efficiently if the reacting chromophore is in the γ-position, consistent with the results found with esters (discussed earlier). A study by Givens and Oettle[124] established this feature for γ-lactones by employing a series of α-, β- and γ-phenyl-γ-butyrolactones[124]. Irradiation of **152** gave CO_2 and phenylcyclopropane (**183**), whereas neither CO_2 nor phenylcyclopropane were found upon irradiation of the α- or β- derivative (equation 91). The efficiency of the cyclopropane product formation can be



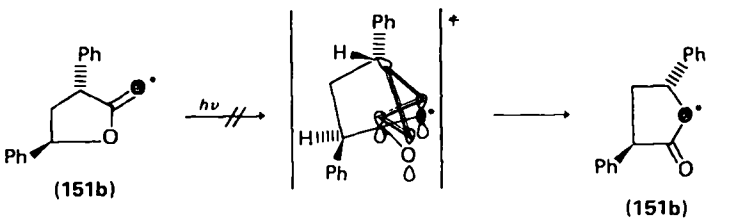
(152) **(183)** (91)

(Φ, 0.026) (Φ, 0.009)

R^1 = H, R^2 = Ph
R^1 = Ph, R^2 = H

enhanced, however, by substitution at both the γ- and α- positions as illustrated by lactones **151** and **153**. While the efficiencies for photodecarboxylation for α-phenyl and α-cyano-γ-phenyl-γ-butyrolactone are not changed significantly by substitution (Φ_{CO_2} = 0.026 and 0.100, respectively), the cyclopropane yield is improved considerably ($\Phi_{R'\_\Delta\_R}$ = 0.020 and 0.077, respectively). The lack of stereospecificity is also illustrated by these lactone reactions. The product mixture from irradiation of either *cis*- or *trans*-α,γ-diphenyl-γ-butyrolactone (**151a** and **b**) was composed of an approximately equal mix of the isomeric 1,2-diphenylcyclopropanes.

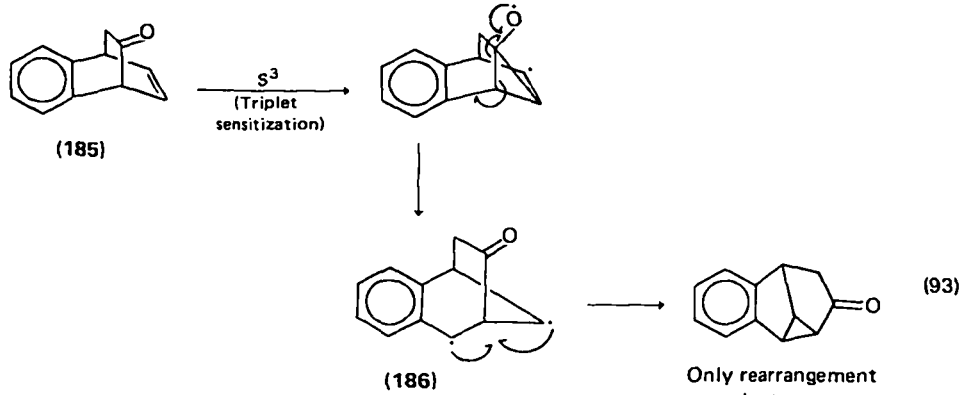
Oxygen-18 and stereochemical studies have been carried out on the diphenyl lactones **151a** and **b** as an extension of the studies with benzyl and naphthylmethyl esters[135] (*vide supra*). The scrambling, which was best rationalized on the basis of a $\pi^2s + \sigma^2s$ suprafacial migration of the ether carbon for the esters, does not occur for the lactones. Equation (92) illustrates the migration, which would require the



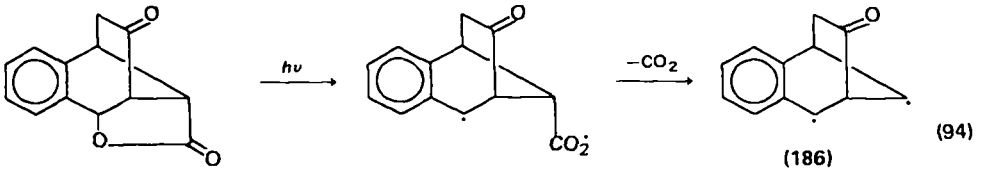
(151b) **(151b)** (92)

highly strained transition state shown for the lactones. Other rationales can be advanced, but the restrictions on any alternative for the scrambling reaction must include: (*i*) no stereochemical equilibration of the migrating carbon; (*ii*) ^{18}O interchange occurring for the esters only, not the lactones.

As with the benzyl and napthylmethyl esters, radical intermediates are implicated in the decarboxylation steps. The lack of stereospecificity in conjunction with the good yields of cyclopropanes is consistent with the diradical mechanism. Attempts to trap ionic intermediates by irradiations in nucleophilic solvents such as methanol gave only the cyclopropanes and no solvent addition product[124]. However, an interesting rearrangement was found for one of the lactones examined by Givens and Oettle[124,145]. In a study designed to test for the intermediacy of a diradical in the oxa-di-π-methane rearrangement[146] of benzobicyclo[2.2.2]-octadienone (185) (equation 93), lactone 148 was irradiated[117,145]. Based on the current understanding of photodecarboxylation of γ-phenyl-γ-butyrolactone, the pathway expected for photolysis of 148 should lead to the common diradical intermediate 186 (equation 94).



(93)

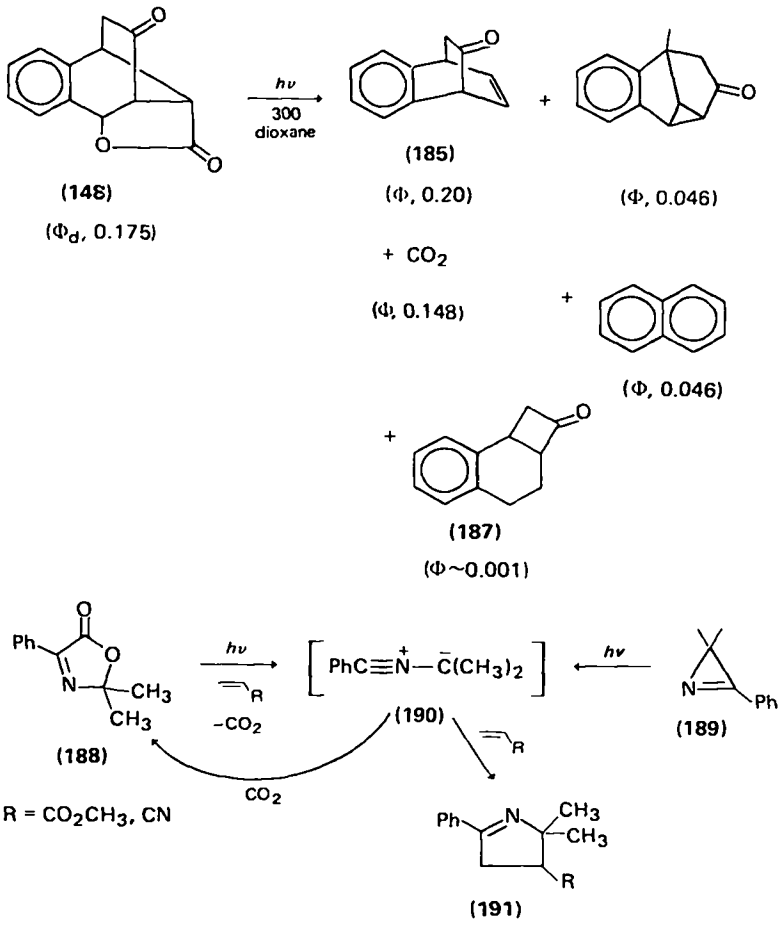


(94)

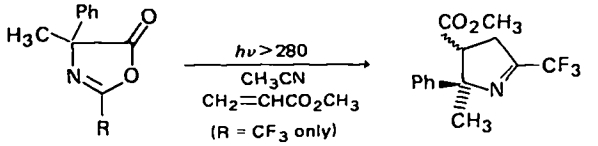
However, as shown in equation (95), an additional product was observed from the decarboxylation sequence which was not found in the sensitized photolysis of the β,γ-unsaturated ketone 185. The absence of 187 from the sensitized irradiations of 185 was taken as evidence against a common diradical (186) for both mechanisms[117,120,145,146], while the weight of evidence is in favour of the intermediacy of 186 from irradiation of the lactone 148. Although an intermediate like 186 has been[146a–c] and continues to be[146d] advanced for other oxa-di-π-methane rearrangements, it is not involved in the sensitized rearrangement of 185.

A novel application of the photodecarboxylation reaction has been developed by Kaplan and Truesdale[134]. The macrodilactone 167 gives a very good yield of paracyclophane upon extended irradiation in dimethoxyethane. Two sequential extrusion reactions of CO_2 occur photochemically to give the paracyclophane in approximately 70% yield.

Finally, the heterocyclic analogue of γ-butyrolactones, azlactones, have been shown to photodecarboxylate to yield nitrile ylides. These can be subsequently trapped by 1,3-dipolarophiles. Schmid[147] and Padwa[148] have provided recent



examples of this reaction sequence, one of which is shown in equation (96)[148]. The sequence from azlactone **188** to the dipolar addition product **191** is regiospecific. In fact, the specificity for this process closely parallels that found on irradiation of azirine **189**, a clear indication that a common intermediate exists. In addition, the azlactone **188** can be formed from the azirine if the irradiation of **189** is carried out in pentane saturated with carbon dioxide. The decarboxylation process was shown to originate from the singlet state[148].



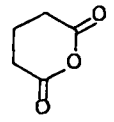
(192) (a) R = CF_3
(b) R = CH_3

In a related study, Johnson and Sousa[149] have shown that Δ^2-oxazolin-5-one (**192a**) also readily photodecarboxylates in the presence of a dipolarophile to give

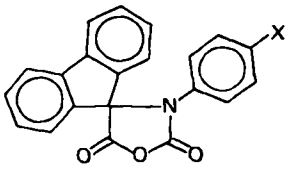
pyrroline (equation 97). In contrast, the methyl-substituted derivative **192b** simply decarbonylates to *N*-(1-methylbenzylidene) acetamide.

C. Anhydrides

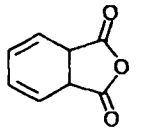
As shown previously, anhydrides extrude carbon dioxide and then carbon monoxide upon irradiation. Most of the examples given in Table 4 (Section B) illustrate loss of both fragments prior to the product-forming step. The four exceptions are **82**, **89**, **94a** and **95**, which also give a carbonyl product resulting



(82)
(Ref. 55)



(89)
(Ref. 47, 49)



(94a)
(Ref. 56)

$PhCH_2CO_2COCH_2Ph$

(95)
(Ref. 57)

from loss of carbon dioxide. The respective products are cyclobutanone, *N*-phenylketenimine, tropone and dibenzyl ketone. Recently a study[57b,c] of substituent effects on the photochemistry of **95** revealed that a third reaction pathway competes with the dibenzyl ketone and dibenzyl formation reactions. With *o*- and *p*-methoxyphenylacetic anhydrides, the formation of *o*- and *p*-methoxy substituted benzyl phenylacetates becomes important. Electron-withdrawing substituents, *m*-substituents, and **95** do not afford appreciable amounts of the ester, however. It appears that this new pathway involves a charge transfer state (an appreciable solvent effect was noted) rather than the radical pathways established for the other products of phenylacetic anhydride. A complete study on substituent effects and the influence of solvents, etc., is needed in order to ascertain the mechanism(s) of these reactions (see Addendum).

V. HYDROGEN ABSTRACTION BY CARBONYL OXYGEN

The abstraction of hydrogen atoms by excited carbonyls is well documented in ketone photochemistry. It is not surprising, then, that this reaction, which has been extensively investigated for ketones, has also been examined with other carbonyl derivatives. In fact, a number of examples have been published over the last two decades which demonstrate the generality of the photochemical hydrogen-abstraction reaction for esters, acids and other related derivatives. Most of the detailed studies have been on esters, so this group will be covered first.

A. Esters

The photochemical hydrogen-abstraction reactions of esters are listed in Table 11. The entries can be conveniently divided into two major groups: (1) intermolecular hydrogen abstractions and (2) intramolecular hydrogen abstractions. Within the second group, subgroupings of two reaction types are apparent: (*a*) *type II* photofragmentation reactions and (*b*) photodeconjugation reactions.

TABLE 11. Hydrogen abstraction by esters

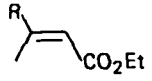
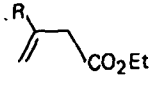
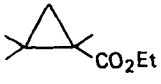
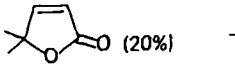
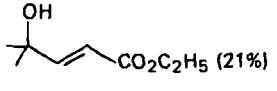
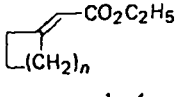
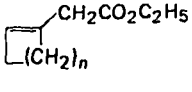
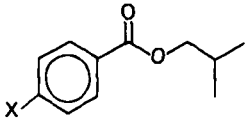
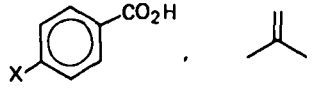
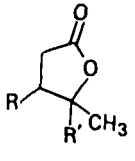
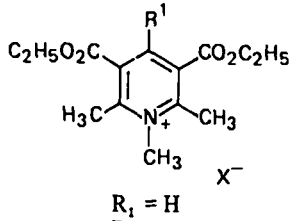
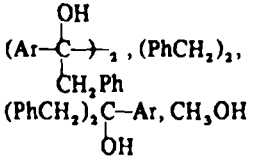
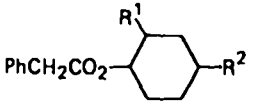
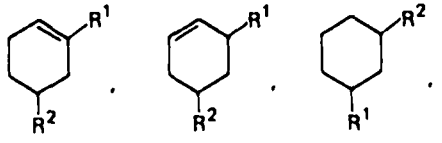
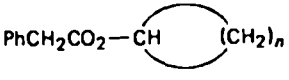
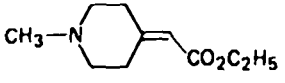
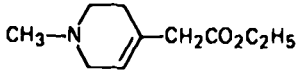
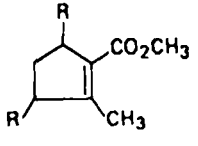
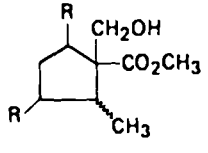
Ester	Conditions[a]	Products (yields)	Reference
(144) Methyl butyrate	Hg, mp, neat liquid	C_2H_4 and others (see Table 8)	61
(146) Ethyl acetate	215–235 nm, gas, liquid and solid	C_2H_4	116
(193)  (a) R = *t*-butyl (b) R = *i*-propyl	Hg, mp, Vycor, ether	 (75%)	150
(193a)	Hg, mp, Vycor, methanol	 (193a)	150, 153, 157
(194) $CH_3CH{=}CHCO_2R$, R = Me, Et (others see text)	>210 nm, CH_3CN or CH_3OH	$CH_2{=}CHCH_2CO_2R$ (20–40%) (*cis–trans* isomerization of 194)	151, 152, 155
(195) $Ph(CH_2)_nCO_2CH_2CH_2OC_2H_5$ (Φ_d, 0.12; *n* = 1) *n* = 0–4	254 nm, hexane	$Ph(CH_2)_nCO_2H$ (Φ, 0.098, *n* = 1) $CH_3CH_2OCH\,CH_2$	154, 161
(196) $HC{\equiv}CCO_2Et$	254 nm, $(CH_3)_2CHOH$	 (20%)  (21%)	156
(197) Methyl *trans*-hepta-2,6-dienoate	Hg, mp, Vycor, methanol	Methyl *cis* and *trans*-hepta-3,6-dienoate (93%, ratio 3:7)	158
(198)  *n* = 1–4	Hg, mp, Vycor, hexane		159

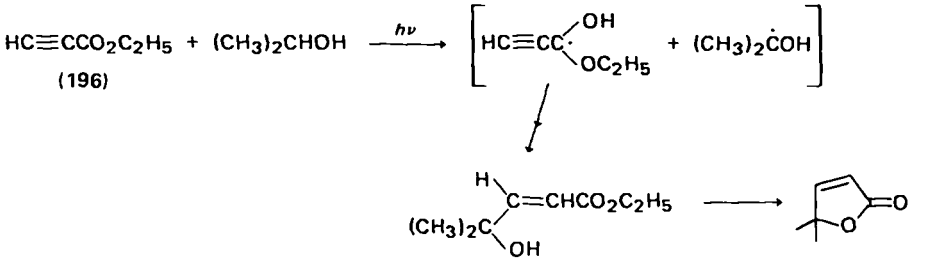
TABLE 11. (Continued)

	Ester	Conditions[a]	Products (yields)	Reference
(199)	Diethyl *trans*, *trans*-deca-2,8-diene-1,10-dioate	Hg, mp, Vycor, methanol or hexane	Diethyl *trans*, *trans*-deca-3,7-dienoate	160
(200)	*threo*- and *erythro*-3-Methyl-2-pentyl *p*-methoxybenzoate, phenylacetate and acetate	254 nm, quartz, pantane or acetonitrile	*p*-Methoxybenzoic acid (Φ, 0.011), *Z*- and *E*-3-methyl-2-pentene; no *erythro–threo* interconversion	162
(201)	2-Methoxyethyl cyclohexanecarboxylate (Φ_d, 0.12)	254 nm, quartz, acetonitrile	$C_6H_{11}CO_2H$ (Φ, 0.11)	163a
(202)	2-methoxyethyl benzoate (Φ_d, 0.013)	254 nm, quartz acetonitrile	$PhCO_2H$ (Φ, 0.011)	163a
(203)	(–)-2-methylbutyl benzoate (Φ_d, 0.004)	254 nm, quartz neat or acetonitrile	$PhCO_2H$ (Φ, 0.004), 2-methyl-1-butene (Φ, 0.0026)	163b
(204)	 (a) X = H (b) X = MeO (c) X = CN (d) X = HO (e) X = K^+O^-	254 nm, acetonitrile		164
(205)	$RCH{=}CHCO_2CH_3$ R = H, CH_3, CO_2CH_3	Hg, Vycor, isopropanol or ethanol	 (R′ = H, CH_3)	165
(206)	 R_1 = H R_1 = CH_3	254 nm, CH_3OD	Deuterium incorporation	165

(162) 1- or 2-Adamantyl phenylacetate	254 nm, CH_3OH	[Adamantene] (~1–2%) and others (see Table 8)	126
(206) $ArCO_2CH_3$	Hg, mp, Pyrex toluene (*p*-cymene)		167
(207)  (a) R_1 = H, R_2 = *t*-butyl (b) R_1 = CH_3, R_2 = H	254 nm, quartz, hexane, (others)	 $(PhCH_2)_2$, CO_2, CO	168a
(208)  n = 4–11	254 nm, quartz, hexane	*cis*- and *trans*-Cycloalkene (Φ, 0.06–0.13)	168b
(209) 	254 nm, Vycor, CH_3OH		169
(210)  (a) R = H (b) R = CH_2CH_3	Hg, mp, Vycor, CH_3OH		170
(211) Alkyl butyrates and valerates	254 nm, Vycor, Hg-sensitized	Alkenes	171
(212) Methyl (+)-O-methylmandelate (Φ_d, 0.17)	254 nm, quartz, CH_3OH	Methylphenylacetate (Φ, 0.084) and racemization of **212** (Φ_{rac}, 0.09)	172
(213) $ArCO_2CH_2CH_2NR_2$	254 nm, cyclohexane	$ArCO_2H$ (Φ, 0.2)	173

[a]See Table 3 for format.

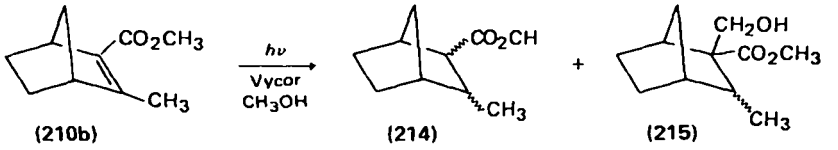
For intermolecular hydrogen abstractions (group *1*), the number of examples is limited[156,165,180]. Ethyl propiolate (**196**), when irradiated in isopropyl alcohol, abstracts a hydrogen atom from the solvent to yield the propargyl radical. Coupling of this with the 2-hydroxy-2-propyl radical yielded the observed hydroxy ester which, upon cyclization, gave the unsaturated γ-butyrolactone (equation 98)[156].



(98)

Irradiation in cyclohexane or ethanol also gave solvent incorporation products, though generally the mixtures were more complex and the isolated products were obtained in considerably lower yields. A similar study on dimethyl maleate, dimethyl fumarate and methyl crotonate in isopropyl alcohol also gave substituted γ-butyrolactones in excellent yields (50–70%)[165].

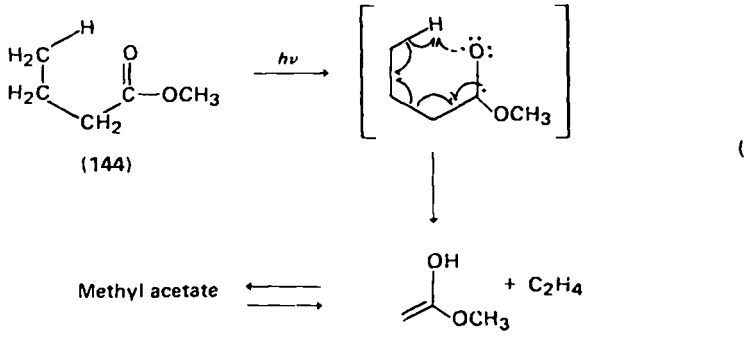
A series of cyclopentenyl carboxylic esters were also shown to yield photoreduction products in methanol. For example, **210b** gave two reduction products **214** and **215** in a 1:2 ratio (equation 99). However, attempts to demonstrate this



(99)

type of reactivity for larger-ring α,β-unsaturated esters led to photodeconjugation reactions (*vide infra*) or to ionic addition products[151,174].

A larger number of studies have shown that intramolecular hydrogen-abstraction reactions occur for esters (group 2*a*, above), analogous to the *type II* γ-hydrogen-abstraction reactions for ketones, which lead to fragmentation. Borrell and Norrish[61] provided one example in the study of the photolysis of butyric acid derivatives discussed earlier. Methyl butyrate (**144**) gave an appreciable amount of ethylene as well as several other products. The ethylene was probably formed by a *type II* reaction as illustrated in equation (100). In this study, the formation of



(100)

TABLE 12. Temperature dependence of labelled ethylene from irradiation of 1,1,2,2-tetradeuterioethyl acetate[a]

T(K)	Ethylene (cc/min)	Ratio C_2D_4/C_2D_3H
322.5	3.00	2.35
302.5	2.88	2.56
273.0	2.46	3.07
270.0	2.40	3.10
244.0	2.20	3.70
224.0	2.09	4.50
198.0	1.72	5.95

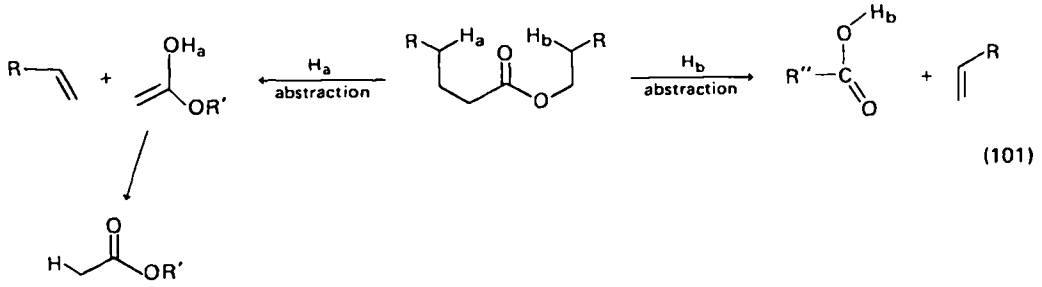
[a]Reprinted with permission from P. Ausloos and R. E. Reppert, *J. Phys. Chem.*, 67, 163 (1963). Copyright by the American Chemical Society.

ethylene could not be sensitized with mercury implying a singlet-state reaction. However, recent studies by Ausloos[116] and Scala[171] have shown that a triplet *type II* reaction is probable (*vide infra*).

γ-Hydrogen abstraction from the alcohol portion of the ester was also noted early. Ausloos[108,110,116] investigated the *type II* reaction for ethyl acetate and found an isotope effect for the hydrogen-abstraction step. Liquid-phase irradiations of $CH_3CO_2CD_2CD_2H$ gave mixtures of C_2D_4 and C_2D_3H. The ratio of C_2D_4/C_2D_3H was shown to depend on the temperature (Table 12) but not on the wavelength (between 215 nm and 235 nm)[116]. A plot of $1/T$ vs $\log C_2D_4/C_2D_3H$ gave an apparent activation energy difference of 1.0 kcal/mol between C–H and C–D abstraction by the excited carboxyl group.

The lower reactivity of the C–D bond leads, in part, to an increased lifetime for the excited carboxyl group. This is demonstrated by irradiation of 1:1 mixtures of ethyl acetate and perdeuteroethyl acetate ($CH_3CO_2CD_2CD_5$) where the ratio of C_2H_4/C_2D_4 increases by a factor of 3.8 upon addition of 2% (v/v) biacetyl[116].

These two examples illustrate the complexity of the *type II* reaction of esters. Fragmentation involving the alcohol portion (H_b) gives rise to a carboxylic acid and an olefin, while fragmentation of the acid moiety (H_a) leads to an acetate derivative and an olefin (equation 101). Both reactions have been examined in detail for intermediates, relative reactivities, and in some cases for the stereospecificity.



(101)

Scala[171] has shown that the relative γ-C–H bond dissociation energies are the major factors determining the direction of the *type II* reactions from mercury-sensitized irradiations. Employing a series of alkyl butyrates and valerates, he was able to establish that the hydrogen-abstracting reactivity correlated with the thermodynamic bond dissociation energies (BDE) according to the following

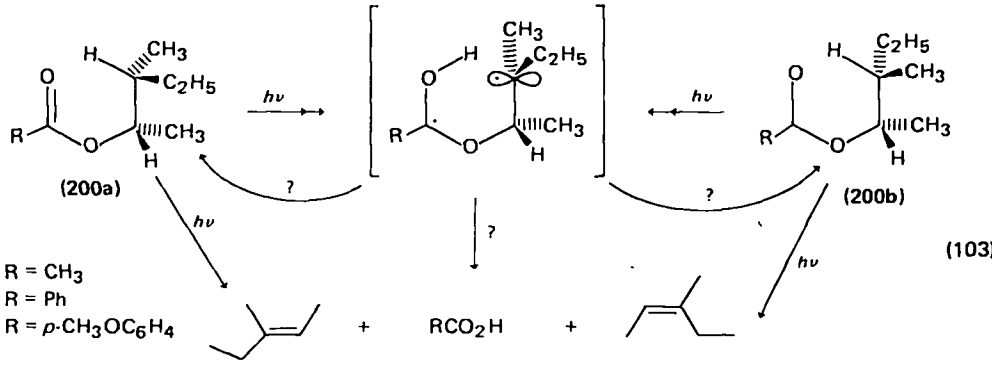
relationship:

$$\frac{\Phi_A}{\Phi_B} = A\left(\frac{N_A}{N_B}\right) \exp(-\beta\Delta(\text{BDE})/RT) \tag{102}$$

where Φ_A, Φ_B are the efficiencies of olefin formation, A is the ratio of the two pre-exponential factors for the two modes of cleavage,
N_A, N_B are the statistical corrections for available γ-hydrogens, and
β is the fractional contribution to the activation energy from the bond dissociation energies (BDE).

A linear correlation of $\ln(\Phi_A N_B/\Phi_B N_A)$ vs $\Delta(\text{BDE})/RT$ gave a slope (β) of 0.30 ± 0.03 and a value for $A = 0.34 \pm 0.007$ from the intercept. From similar treatments ketones (β, 0.45; A, 0.84)[171,175], carbonates (β, 0.05; A, 1.04)[171] and thiocarbonates (β, 0.17; A,0.99)[171] indicate that both bond dissociation energies and the atoms adjacent to the carbonyl play a significant role in the photochemistry for the ester reactions only. As determined from the ester preexponential A value, H_a abstraction is favoured by a factor of 3 over H_b abstraction. Implicit in these analyses are the assumptions that once the hydrogen is abstracted it does not return, and that all of the reactions have the same efficiency of energy transfer within each series of reactants. Evidence in support of the second assumption is the exothermicity of energy transfer from ^{3}Hg (112 kcal/mol), which should be sufficient to assure unit efficiency for triplet energy transfer for all of the functional groups examined.

The irreversibility of the hydrogen-abstraction step is not as well established, although it has been independently examined in a number of studies. Gano[162] has examined a number of diastereomeric esters in quest of evidence for the reversibility of the hydrogen-abstraction process. Studies of *threo* and *erythro* esters **200a** and **b** revealed no interconversion, even in high conversion photolyses for the acetates, and only a modest interconversion with the phenylacetates (equation 103). The *threo* and *erythro* acetates and phenylacetates gave ratios of *Z*- and



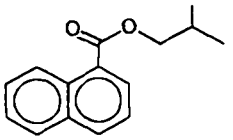
(103)

E-3-methyl-2-pentenes which reflected the reactant stereochemistry. The *Z*/*E* ratios from *threo* acetate and *threo* phenylacetate were 3.2 and 3.8, with the phenylacetates showing a little more selectivity. A similar result was found for the *erythro* isomers where *Z*/*E* ratios were 0.85 and 0.37. These ratios suggest that a diradical intermediate which has time to equilibrate intervenes before product formation. Attempted quenching experiments were successful only with quenchers like

oxygen, which also quenched the esters' fluorescence, suggesting a reactive singlet excited state[162].

Another attempt to demonstrate significant reversibility for the hydrogen-abstraction step was a study by Pacifici and Hyatt[163] on the irradiation of (−)-2-methyl-1-butyl benzoate (**203**). The major process was γ-hydrogen abstraction to yield 2-methyl-1-butene and benzoic acid. The efficiencies of product formation (4×10^{-3}) and racemization of the ester (2.6×10^{-3}) are nearly the same, in contrast with Gano's findings. Pacifici and Hyatt[163] did establish singlet-state reactivity for the benzoate elimination by lack of quenching with piperylene. Interestingly, a study of 2-ethoxyethyl benzoate and cyclohexylcarboxylate differed in this respect. Elimination occurred from the singlet for the aliphatic ester and from the triplet for the aromatic derivative. Thus, it appears that both singlet and triplet states are reactive and that the nature of the process is very sensitive to the structural features of the ester. No complete analysis of this parameter is currently available.

One parameter that has been investigated is the proximity of the aromatic chromophore and the ester in bichromophoric esters. Morrison[154,161] found that for $Ph(CH_2)_nCO_2R$, only for $n = 1$ was significant photoreactivity observed. Again, singlet reactivity was established. The 1- and 2-naphthylacetates were also shown to be unreactive. The clear implication from these and earlier studies is that the reactivity of the excited state is sensitive to the total energy available. In most cases, the singlet state is the only one of sufficient energy to allow efficient C–H bond cleavage. This contrasts sharply with the ketone *type II* reaction where lower-energy, longer-lived triplets also compete for the γ-hydrogen[1,76]. Employing a systemic variation in the aromatic acid moieties (for $n = 0$) Barltrop and Coyle[164] determined the rate of acid and olefin production for each derivative (**204** a–e). Quenching studies revealed little quenching for all but the phenoxide salt. The reactivities of **204e** and of the naphthyl ester **216** were totally quenched



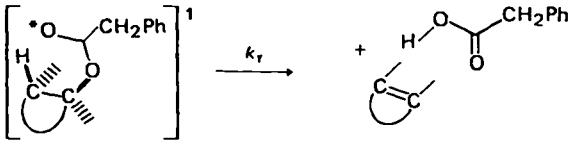
(216)

with added piperylene or biacetyl. For this *type II* reaction, the quantum efficiencies for all of the esters were very low, ranging from 0.01 to 0.001. Barltrop contended that the reactive excited states have the lowest n,π^* configuration for the singlet and a π,π^* configuration for the triplet. For ketones the n,π^* states are considerably more reactive (ten times) than the π,π^* states[177]. It follows then that the lower reactivity of esters was due to a combination of the unfavourable singlet–triplet splitting, yielding a lowest π,π^* triplet (less reactive), and the short lifetime of the lowest lying n,π^* singlet, which may also have considerable π,π^* character.

Despite its inefficiency, this reaction, which is the photochemical analogue of ester pyrolysis, has been applied to the syntheses of a number of olefins. A recent example is Gano's reported synthesis of adamantene in low yield from 1- or 2-adamantyl phenylacetate[126] (**162**, Table 8). The highly strained bridgehead double bond generated on photolysis of **162** reacts with electrophiles to give 1-substituted adamantanes.

A more extensive study of the *type II* reaction as an elimination reaction has

come from the work of Yarchak, Dalton and Saunders[168]. Quantum-yield and stereochemical studies have shown that the availability of the γ-hydrogen correlates with the efficiency of the reaction. Two parameters, ring-size effects and β-substitution, were explored. With variation of the ring size, the γ-hydrogen's approach to the ester carbonyl is controlled by the conformational parameters of each ring, which can be independently examined (equation 104). A plot of ring size



(104)

vs efficiency is given in Figure 11 for photolysis of phenylacetates and for the pyrolysis of amine oxides[178] (also a *syn* elimination). A comparison of the two reactions illustrates their similar steric demands in the small-ring compounds. The differences noted for the medium-sized rings can be attributed in part to their conformational flexibility and in part to the difference in conditions (solvent, temperature) between the two studies. The requirement that the elimination be *syn* is based on the study of the photolysis of *cis*- and *trans*-2-methylcyclohexyl phenylacetates (**207b**). The *cis* isomer yields a 10:1 ratio of 3-methylcyclohexene: 1-methylcyclohexene while the *trans* isomer gives a 1:1 mixture of the two cycloalkenes. Also, *cis*-4-*t*-butylcyclohexyl phenylacetate (*cis*-**208a**) photofragments three times more efficiently than the *trans* isomer (*trans*-**208a**), a definite conformational bias for *syn* elimination[168]. Again, singlet-state reactivity was established (see Addendum).

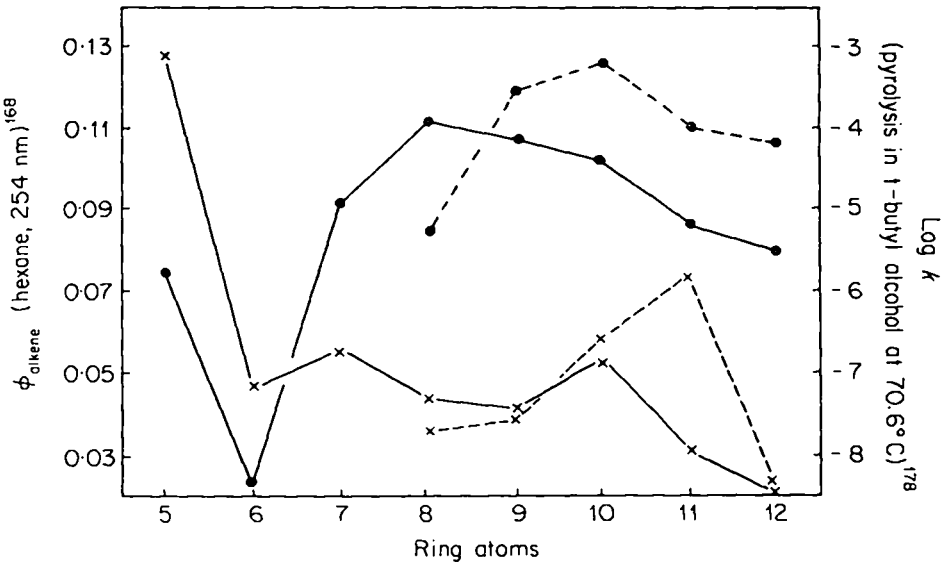
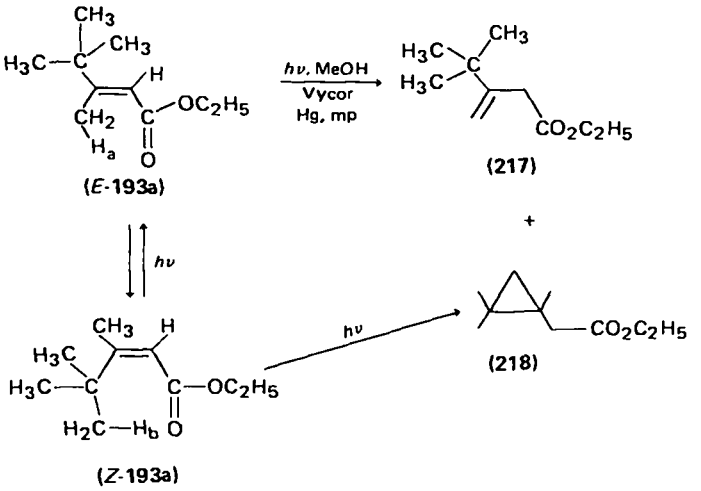


FIGURE 11. Ring-size effects on the photolysis of cycloalkyl phenylacetates and cycloalkyldimethylamine oxides: ––– *trans*-cycloalkene, —— *cis*-cycloalkene, • pyrolysis, x photolysis. Adapted from Figures 1 and 2 in Reference 168b. Reproduced by permission of the American Chemical Society.

In summarizing these varied studies of the ester *type II* process, one can conclude that phenylacetate esters undergo the most efficient reactions. The high energy of the n,π^* singlet, which may involve both chromophores either through energy transfer or direct interaction, appears to be the reason for the increased reactivity of this ester derivative over others examined. Requirements for the γ-hydrogen have not been extensively explored, though the results available tend to confirm a behaviour parallel to that in ketone *type II* reactions[176].

The third major area involving ester carbonyl hydrogen abstractions is the photodeconjugation reaction of α,β-unsaturated esters (group *2b*, above). The pioneering work of Jorgenson and coworkers[150,153,157] went far in establishing the scope and nature of this process. An early example was the photodeconjugation of ethyl *E*-3,4,4-trimethyl-2-pentenoate (**193a**) in methanol. This reaction is particularly intriguing because of the side-reaction discovered for this isomer only. Thus, **193a** yields two products, the β,γ-unsaturated ester **217** and the cyclopropyl ester **218** (equation 105). A rapid photoisomerization of the double bond allows

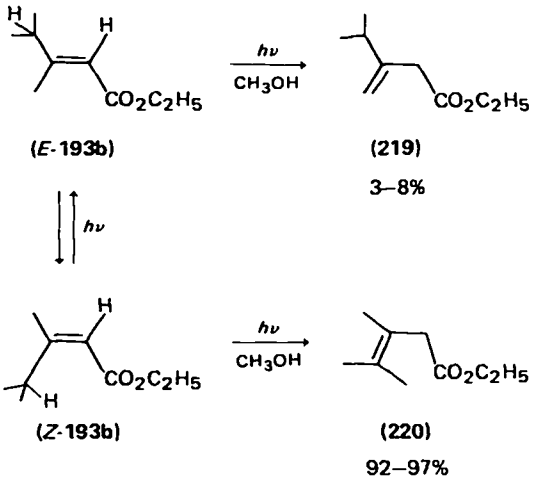


(*E*-193a) (217) + (218) (105)

(*Z*-193a)

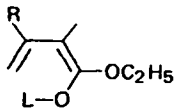
access to the δ-hydrogen by the carbonyl. Once this equilibration has been established, the efficiency for **218** formation is approximately equal to the deconjugation efficiency.

No cyclopropane is formed from ethyl-3,4-dimethyl-2-pentenoate (*Z*-**193b**), which yields only the two expected β,γ-unsaturated esters **219** and **220**[150,153] (equation 106). The formation of **219**, which involves the abstraction of a primary hydrogen, is in less than 10% yield. A dramatic increase in that yield is noted when the reaction is performed in methanol-*O*-d; the yield of **219** rises to as high as 60% of the deconjugated products[157]. The solvent isotope effect is exclusively centred on the formation of **219** for no effect was noted on the efficiencies of **220** formation and on the *Z*–*E* photoequilibration of **193**. A low incorporation of deuterium for both products was noted; however no details are available concerning the incorporation of deuterium in the reactant or the overall efficiency of the photodeconjugation process. This intriguing solvent isotope effect (which is estimated to be between 15 and 50 for **193b**) was also noted for the reaction of **193a**, where the efficiency of **217** formation is enhanced by a factor of 13 in methanol-*O*-d. The isotope effect is most likely due to the effect on the relative rates of protonation of the α- and γ-carbons of the intermediate dienol **221**, though



(106)

insufficient information is available to confirm this suggestion[157]. It is noteworthy that the yield of deconjugation product is enhanced by the solvent change to methanol-*O*-d, a point that may be of value in synthetic studies.



(221) L = H or D

A number of other photodeconjugation studies have been reported and appear in Table 11. Most of the authors suggest that the evidence available favours an n,π^* singlet-state abstraction process for the deconjugation reaction[152,160], consistent with the findings for the *type II* process discussed earlier.

B. Other Carbonyl Hydrogen-abstraction Reactions

The hydrogen-abstraction processes observed for excited esters have also been sought for other derivatives of carboxylic acids. Table 13 lists a variety of examples for which the primary process is believed to be a hydrogen-atom abstraction by an excited carbonyl. The entries in Table 13 are for the carboxylic acids, lactones and imides which have been examined in some detail.

In his early study of the photochemisty of butyric acid derivatives (see Section IV.A), Norrish also examined butyric and isobutyric acid[61]. Butyric acid (**105**) undergoes a *type II* process of high efficiency ($\Phi = 0.17$), which could not be quenched with oxygen, could not be sensitized by mercury and was generally insensitive to a modest temperature change (0–80°). Isobutyric acid, which possesses no γ-carbon, gave no products of the *type II* elimination process[61].

This same γ-hydrogen-abstraction process was also observed in the photodeconjugation of α,β-unsaturated acids. Sorbic acid (**222b**) was converted into the

TABLE 13. Other carbonyl hydrogen-abstraction reactions

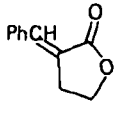
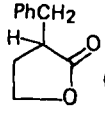
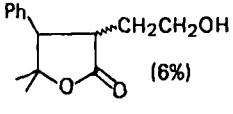
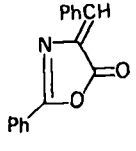
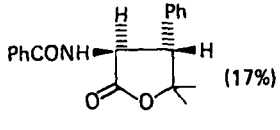
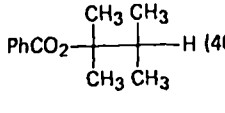
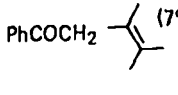
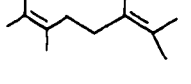
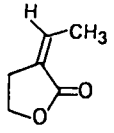
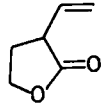
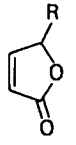
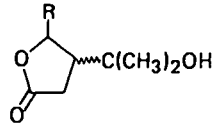
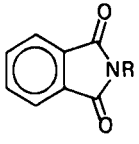
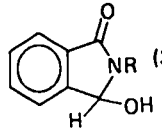
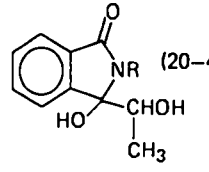
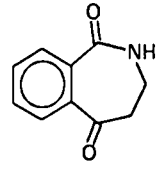
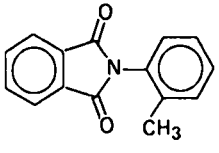
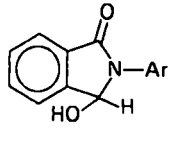
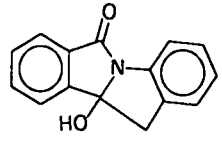
Substrate	Conditions[a]	Products	Reference
(105) $CH_3CH_2CH_2CO_2H$	Hg, hp, 235–250 nm vapour phase, isooctane	CH_2CH_2 (Φ, 0.17)	61
(222) $RCH{=}CH{-}CH{=}CHCO_2H$ (a) $R = CH_3$ (b) $R = H$	Hg, mp, Vycor ether	$RCH{=}C{=}CHCH_2CO_2H$ (a) (20%) (b) (32%)	179
(194) $CH_3CH{=}CHCO_2H$	Hg, mp, Vycor methanol	$CH_2{=}CHCH_2CO_2H$ (59%)	151
(223) $RCH_2CH{=}CHCO_2H$ $R = n\text{-}C_6H_{13}, n\text{-}C_7H_{15}, n\text{-}C_{12}H_{25}$	Hg, lp, quartz methanol, hexane or pentane	$RCH{=}CHCH_2CO_2H$ (*Z*/*E*, 0.5) (95%)	155
(224) 	Hg, hp, Vycor isopropyl alcohol	 (6%),  (6%) and 2 others (unidentified)	180, 184
(225) 	Hg, mp, filter, 254 nm isopropyl alcohol	 (17%)	180, 184
(102) CH_3CO_2H	?, 230–250 nm, (monochromator), R_2CHOH	$R_2\dot{C}OH$ (e.s.r.)	68
(108) $PhCO_2H$	Hg, mp, ?, 1% sol in 15% 2,3-dimethyl-2-butene in hexane	 (46%), $PhCOCH(CH_3)_2$ (22%) $PhCOCH_2$  (7%) + ,  (25%)	181

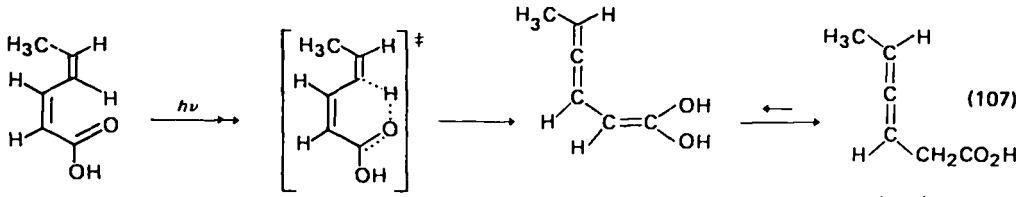
TABLE 13. (Continued)

Substrate	Conditions[a]	Products	Reference
(226) 	Hg, hp, Pyrex acetonitrile	 (27%)	182
(227)  (a) R = H (b) R = CH_3	Hg, lp (254 nm) isopropyl alcohol	 (a) (90%)	183
(228)  (a) R = CH_3 (b) R = C_2H_5 others (see text)	Hg, hp, ? ethanol, acetonitrile or *t*-butanol	 (30–40%),  (20–40%)  (69%) (for b only)	185
(229) 	Hg, hp, ? ethanol	 (20%)  (65%)	185

(230)	(Φ_d, 0.005)	Hg, mp, Pyrex, −15°C, isopropyl alcohol	(57%) (*meso*/*d*,*l* = 3:2)	186
(231)		Hg, mp, Pyrex, isopropyl alcohol	230 (44%), propene	186
(232)		Hg, mp, Pyrex, benzene	(40%)	187

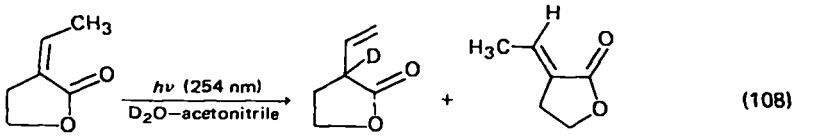
[a]See Table 3 for format.

allene carboxylic acid 233 in 20% yield by a γ-hydrogen-abstraction followed by proton tautomerization[179] (equation 107).



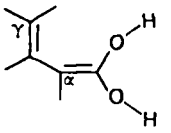
(222b) (233) (107)

Other examples of photodeconjugation of acids have been reported by Kropp[151] and by Doering[155] (see 194 and 223, Table 13). Deconjugation of the exocyclic α,β-unsaturated lactone 226 provides a route to allyl lactone 234[182]



(226) (234) (108)

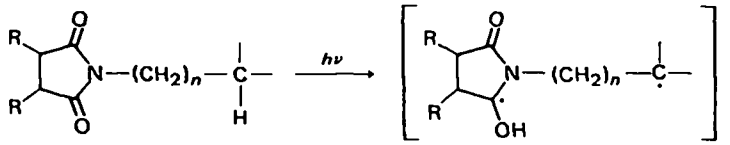
(equation 108). The reactions have been characterized as high-yielding, synthetically useful processes which are generally free of complicating side-reactions. The advantage of photochemical deconjugation over catalytic methods rests in the fact that the product ratio of α,β/β,γ unsaturated acids is not controlled by the thermodynamic stability of the two acids, but by their absorptivities, and to a lesser extent, by the relative rates of α- vs γ-protonation of the diene-*gem*-diol 235.



(235)

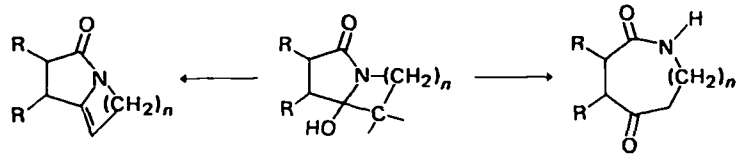
An extensive study of the *type II* reactions of imides has been conducted by Kanaoka and his coworkers[80,185a–i]. In a fascinating series of papers, Kanaoka[185] has unveiled an intramolecular hydrogen-abstraction reaction of imides such as 228 and 229 which appears to be as general as the *type II* reactions of ketones. Although there are some parallel features in the ketone and imide photoreactions, the differences between these two funtionalities are noteworthy. For example, the δ-hydrogen (the origin being designated as the imide carbonyl) is more efficiently abstracted than the γ- or ε-hydrogen. This feature excludes an efficient path to fragmentation and ensures the dominance of other diradical reactions. For the imides, the principal pathway appears to be cyclization to the bicyclic hydroxy lactams 237 (equation 109). Several of the hydroxy lactams were unstable, and either water was eliminated to yield the unsaturated lactam (238) or a fragmentation reaction occurred to give a ring-expanded keto lactam (239). Several selected examples which illustrate the generality of this new reaction are given in equations (110)–(112). The isolated yields were not consistently high; nevertheless, the potential usefulness of this reaction is evident.

Very little mechanistic work has been reported on the reaction. Neither the

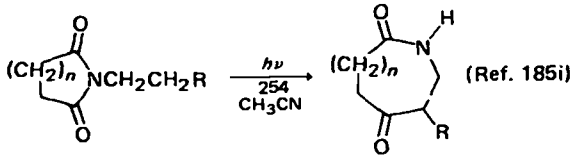


(228) R = C_6H_4
(236) R = H

(109)



(238) (237) (239)

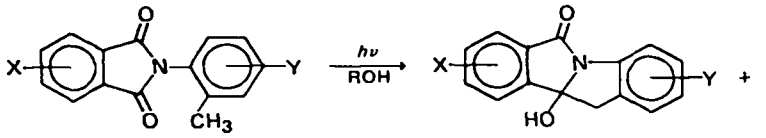


(240) (241)

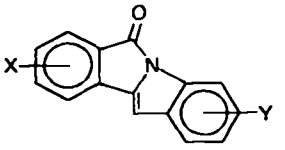
n = 1,2
R = H, CH_3, C_2H_5

33–56%

(110)



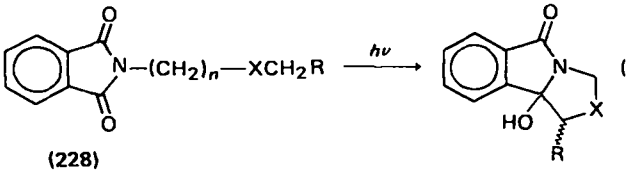
(229) (242)



(243)

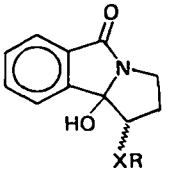
(111)

229	242 and/or 243 (after 2.5 h)
(a) X = H, Y = H	65%
(b) X = 3-Cl, Y = H	35%
(c) X = 4-CN, Y = H	21%
(d) X = 4-CO_2Me, Y = H	20%
(e) X = H, Y = 3'-CH_3	62%
(f) X = H, Y = 4'-CH_3	20%
(g) X = H, Y = 4'-OCH_3	29%
(h) X = 4-OCH_3, Y = H	0%
(i) X = H, Y = 4'-NO_2	0%



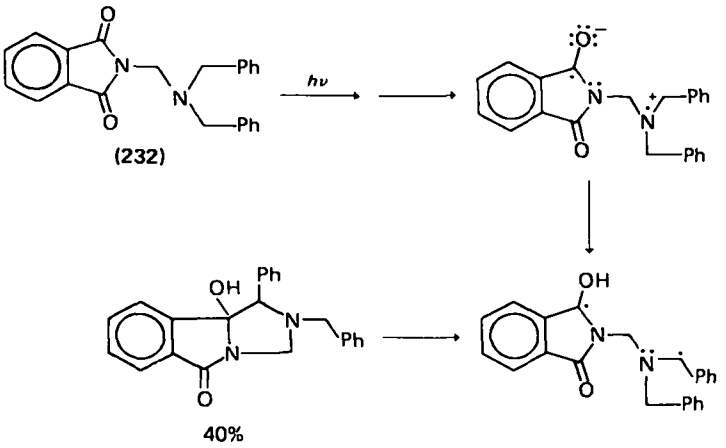
(228) (Ref. 185b, d) (112)

(c) $n = 1$, X = O, R = CH_3 30%
(d) $n = 1$, X = O, R = Ph 60%



(e) $n = 3$, X = O, R = CH_3 80–90%
(f) $n = 3$, X = S, R = $C(CH_3)_3$ 47%

efficiency of the reaction nor the excited-state multiplicity is known. A cursory attempt to delineate the substituent effects on the reaction indicated that electron-donating groups on the aniline moiety increased the product yield slightly. However, substituents on the phthalimide ring generally lowered the product yield. The only conclusion to be drawn from that study is that substituents on the aniline ring appear to stabilize the incipient radical generated by hydrogen-abstraction[185h]. In a recent study by Coyle and Newport[187] on phthalimide (232), a charge-transfer step preceeding the hydrogen-abstraction process was suggested (equation 113).

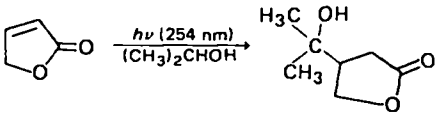


(232) (113)

40%

This reaction could not be quenched by 1.3 M piperylene, indicating a reactive singlet or a very short-lived triplet precursor. This has been taken as evidence that hydrogen abstraction by the phthalimide triplet is unlikely, since the rate of hydrogen abstraction ($10^5 - 10^7$ s^{-1})[188] could not compete with decay by other processes ($> 10^{10}$ s^{-1}).

Hydrogen abstraction from solvent has been observed in several instances. When the α,β-unsaturated lactone **227a** was photolysed in isopropyl alcohol, a 90% yield of **244** was realized[183] (equation 114). This same reaction product could be obtained by including a free-radical chain process with benzoylperoxide. Further-

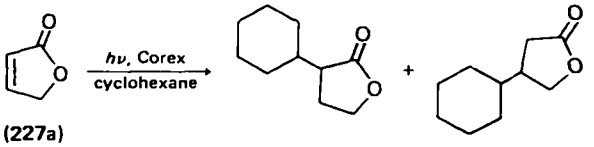


(114)

(227a) (244)

more, quantum-yield measurements indicated a free-radical chain process because of the variation of Φ with the concentration of **227a**, analogous to the concentration-dependent efficiencies for photoreduction of cyclopentenone. The efficiencies varied from 30 to 2.8 with concentrations of **227a** from 0.14 M to 0.796 M[183].

Flechtner[189] and Smith and coworkers[190] examined the photochemisty of **227a** in hydrocarbon solvents. With cyclohexane as solvent, the products obtained were the α- and β-cyclohexyl-γ-butyrolactones in approximately equal yield (equation 115). The formation of the α-isomer is unusual and is suggestive of hydrogen abstraction by the β-carbon of the α,β-unsaturated ester. Analogy for such a process is found in the work of Agosta and Smith with cyclopentenone derivatives[191].



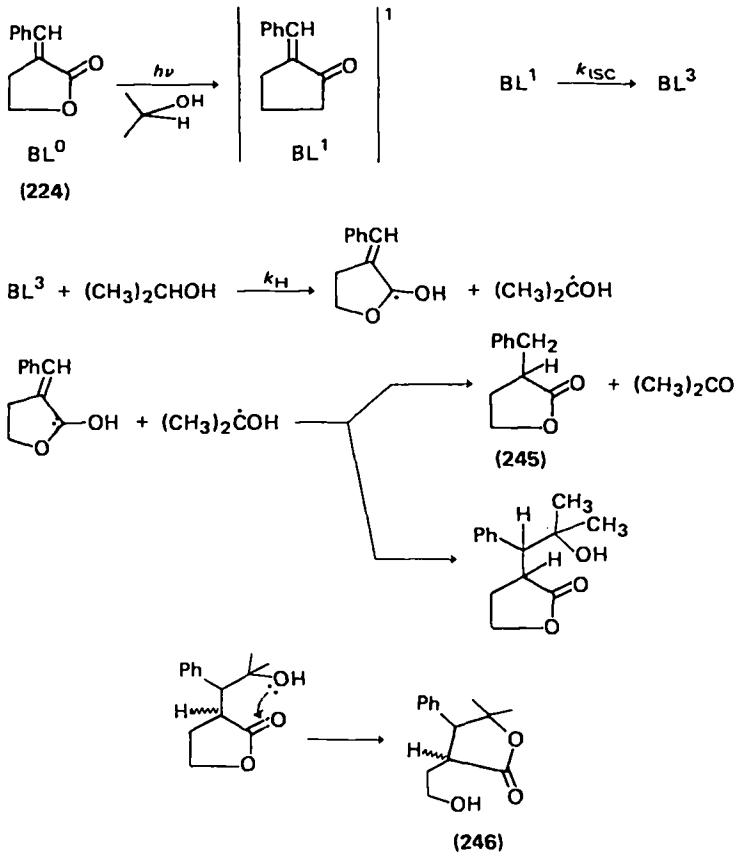
(115)

(227a)

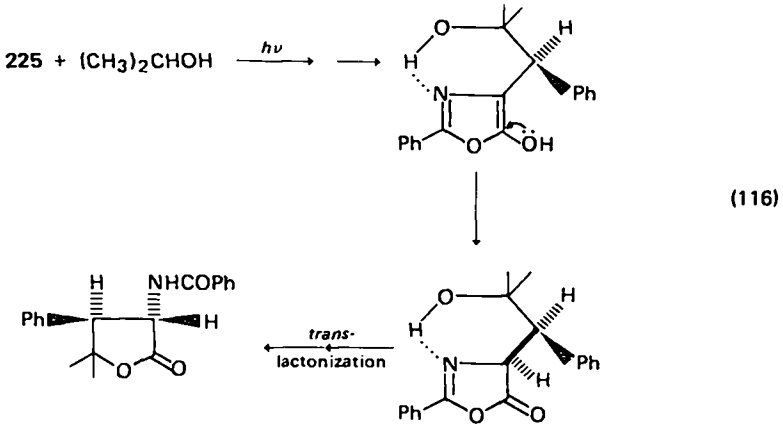
Koch has found a similar photoreaction of imino lactones. Hydrogen abstraction was observed for two cases: abstraction from isopropyl alcohol (solvent) by **230** and intramolecular abstraction from **231**. In the hydrogen-donating solvent, reductive dimerization occurred through the triplet-state manifold. When the *n*-butyl side-chain is present, as in **231**, intramolecular γ-hydrogen-abstraction initiates a fragmentation process by which **230** is formed along with propene. The concentration dependence noted for **231** suggests a bimolecular hydrogen-transfer process, though the evidence was not conclusive[186].

A rare example of wavelength control of the photochemistry of lactones was noted by Ullman and coworkers[180,184]. The benzal derivatives of 5-oxazolone (**225**) and γ-butyrolactone (**224**) showed only $Z \rightleftharpoons E$ interconversion at longer wavelengths (365 nm and 313 nm, respectively). At shorter wavelength (254 nm), geometrical isomerization was accompanied by a less efficient solvent-incorporation reaction. When isopropyl alcohol was the solvent, the major identified photoproducts of benzal-γ-butyrolactone (**224**) were the lactones **245** and **246** (Scheme 8). These were formed by initial hydrogen abstraction followed either by hydrogen-atom transfer to give benzyl-γ-butyrolactone (**245**), or by radical coupling to yield the solvent addition intermediate. *Trans*-lactonization with the new γ-hydroxy function gave the rearranged lactone. A sequence similar to that shown in Scheme 8 is suggested for the solvent-incorporated product from **225**, with the added requirement that the protonation of the enol be stereoselective (equation 116).

The wavelength dependence has been associated with the triplet-state configurations of lactone **224** and oxazolone **225**. At longer wavelength (> 300 nm), only the lowest triplet (T_1) is populated. The configuration is suggestive of π,π^* type since only $Z-E$ interconversion occurs. At higher energies (254 nm), both n,π^* (T_2) and π,π^* triplets are populated, presumably as a result of intersystem crossing from upper singlet excited states. Internal conversion from T_2 to T_1 must be slow, allowing hydrogen abstraction to be competitive.

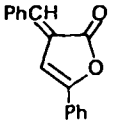

PhCH
hν
OH
H
BL⁰
(224)
PhCH
BL¹
1
BL¹ kISC BL³
BL³ + (CH3)2CHOH kH
PhCH
OH + (CH3)2ĊOH
PhCH2
H
+ (CH3)2CO
(245)
CH3
CH3
Ph
OH
Ph
OH
H
Ph
OH
(246)

SCHEME 8.


225 + (CH3)2CHOH
hν
H
NHCOPh
Ph
H
trans-
lactonization
Ph

(116)

Independent evidence in support of this mechanism was obtained from sensitization studies. Several, but not all, sensitizers of varying triplet energies were found to show selectivity in sensitizing the two processes. For example, with lactone **225** or **247** (which also shows the wavelength-dependent reactivity), benzene, fluorene, biphenyl and napthalene (Table 1) sensitized both reactions, while triphenylene, phenanthrene, *o*-terphenyl and 1-phenylnapthalene sensitized only the *Z–E* interconversion. Triplet sensitizers with triplet energies below 58.4 kcal/mol for **225** and 60.9 kcal/mol for **247** were selective for only *Z–E* interconversion, evidence that the lowest energy triplet is the precursor of this reaction.



(247)

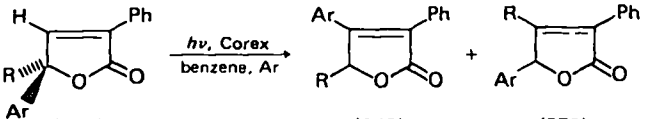
Ullman further suggests that the *Z–E* interconversion from the lower π,π^* triplet is sensitized directly with those sensitizers for which the LUMO of the lactones is matched with the HOMO of the sensitizers, even when the triplet energy of the sensitizer is above T_2. The selectivity is lost if such a correlation cannot be made[180b,c]. Failure to observe the wavelength and sensitizer selectivity for acyclic α,β-unsaturated esters was noted although not fully rationalized[180b] (see Addendum).

VI. REARRANGEMENT AND SOLVOLYSIS REACTIONS

Derivatives of carboxylic acids undergo a variety of photochemical rearrangement reactions, including several interesting carboxyl-group migrations which have recently been reported. Likewise, bond reorganization other than fragmentation after cleavage of the *a*, *b* or *c* bonds (Figure 5) of esters and imides has led to new, isomeric products. In this section a selection of these reactions will be reviewed. A brief survey of photosolvolysis studies on carboxylic acid derivatives is also included in this section. This controversial area of research continues to stimulate new investigations in photochemistry.

A. Photorearrangements

Many esters, lactones, and other acid derivatives undergo photorearrangement reactions which bear a strong resemblance to those of their ketone analogues. Recently, for example, Padwa and Dehm[192a,b] discovered that 5-aryl-2(5*H*)-furanones **248a–f** rearrange to the 4-aryl derivatives **249** as well as to **250** (equation 117).

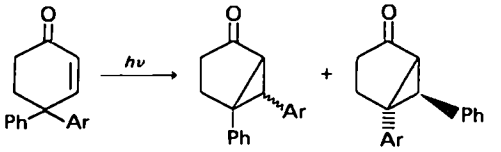


(117)

(248) (249) (250)

(a)	R = H, Ar = Ph	100%	0%
(b)	R = Ar = Ph	78% (Φ, 0.47)	–
(c)	R = Ph, Ar = *p*-$CH_3OC_6H_4$	16 :	1
(d)	R = Ph, Ar = *p*-CNC_6H_4	3.5 :	1
(e)	R = Ph, Ar = *m*-$CH_3OC_6H_4$	1.5 :	1
(f)	R = Ph, Ar = *p*-$CH_3C_6H_4$	3.5 :	1

These reactions show a remarkable parallel to the photochemistry of 4,4-diarylcyclohexenones studied by Zimmerman[193]. The migratory aptitudes of *p*-CN, *p*-CH_3O, *m*-CH_3O and *p*-CH_3–phenyl (as indicated in equation 117) are all greater than phenyl. For the $^3(n,\pi^*)$ state of 4-aryl-4-phenylcyclohexenones **251** a–c, the migratory aptitude of the aryl group was found to be an order of magnitude greater than phenyl for both electron-withdrawing and -donating groups[193] (equation 118). In this study, the stabilization by the *migrating* group was shown to be the

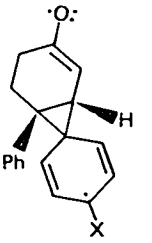


(118)

(251) **(252)** **(253)**

(a) Ar = Ph
(b) Ar = *p*-CNC_6H_4 14 : 1
(c) Ar = *p*-$CH_3OC_6H_4$ 12 : 1

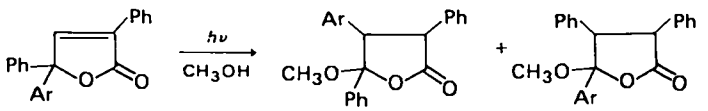
controlling factor. The half-migrated species like **254** possesses a significant fraction of free-radical character on the migrating group and thus is stabilized by either the *p*-CN or *p*-CH_3O substituents.



(254)

For the aryl furanones **248**, the preference for migration of the aryl group was shown to arise from an enhanced rate for aryl migration over phenyl migration from the excited triplet state, as determined by quenching experiments with piperylene. Thus, the triplet-state reactivity is controlled by the 'stabilization of the radical-like free valence by the *migrating* group'[192b]. The furanones also exhibit phosphorescence in ethanol or methylcyclohexane–isopentane glasses at 77 K. The triplet energy and lifetime were determined to be 59 kcal/mol and 170 ms, respectively, and are similar to the values obtained for 1-phenylcyclopentene[194]. It appears that the lactone group does not significantly influence the triplet chromophore suggesting that the energy is localized in the styryl group.

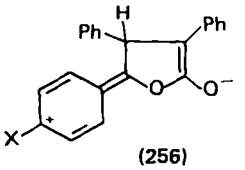
A solvent effect was also noted for this rearrangement[192b]. In methanol, product formation involved the same initial rearrangement step as in benzene but this was followed by nucleophilic addition of methanol (equation 119). These



(119)

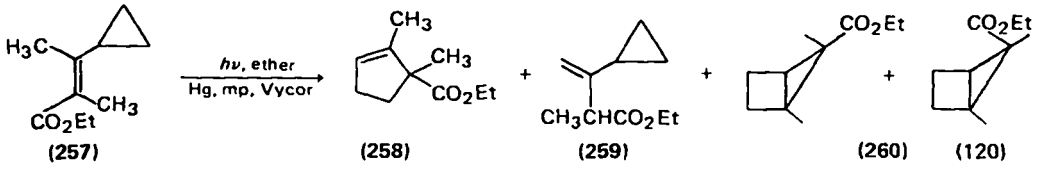
(248b–e) **(255a)** **(255b)**

addition products (**225a** and **255b**) were converted into the same unsaturated lactones **249** and **250** for analysis. Nucleophilic addition by methanol indicated a zwitterionic intermediate in the more polar, hydrogen-bonding solvent. That an ionic intermediate was involved early in the sequence was shown by the change in migratory preferences. For electron-donating groups, the ratio **249/250** was 0.72 for *p*-OCH_3 and 0.81 for *p*-CH_3, while for the electron-withdrawing groups, the ratio was unity or greater. This suggests that in methanol, a zwitterionic-like state for migration is controlling and that the stabilization of the incipient carbonium ion (**256**) becomes important. The change in states from diradical to zwitterionic is expected with a solvent change from non-polar benzene to methanol[195].

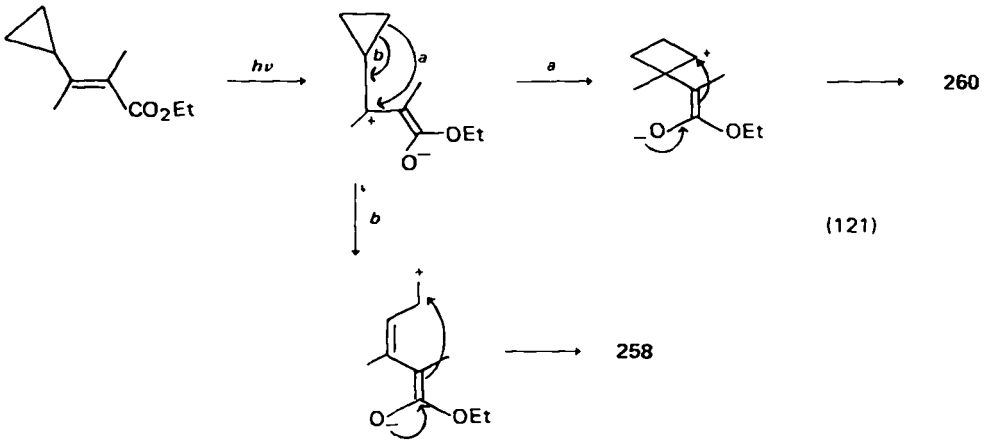


(256)

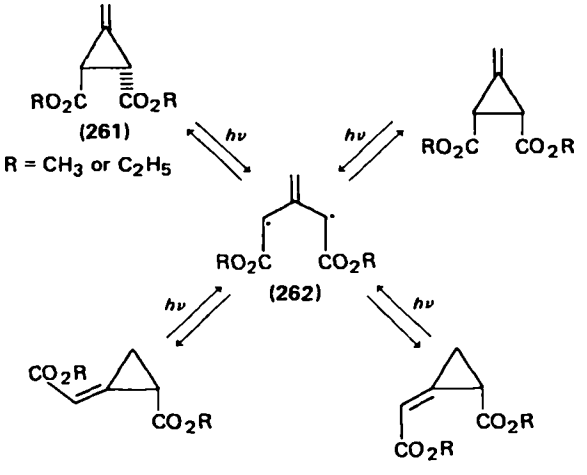
An earlier example of an α,β-unsaturated ester photorearrangement was the formation of the bicyclo[2.1.0]pentane and cyclopentene skeletons from cyclopropylacrylate **257** (equation 120)[196]. Jorgenson[196] found that rearrangement products (**258** and **260**) were formed in addition to the deconjugated isomer **259**, and suggested that a zwitterionic state preceeded rearrangement in this system also. A cyclopropyl carbinyl–cyclobutyl carbonium ion rearrangement was postulated (equation 121)[196].



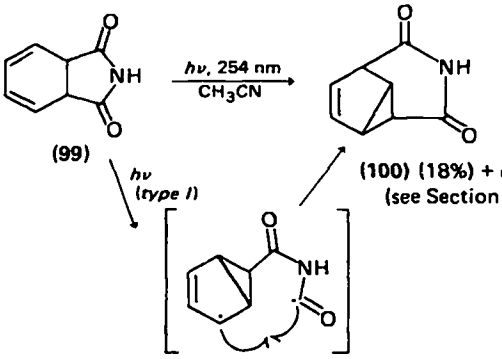
(257) (258) (259) (260) (120)



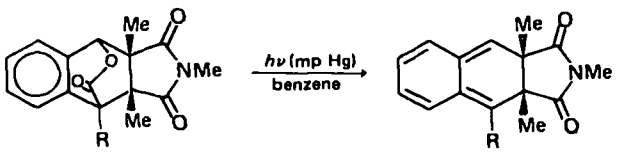
Recently reported β,γ-unsaturated ketone rearrangements[146] have also found a parallel in the photochemistry of acid derivatives. Several notable examples are given in equations (122)–(126).

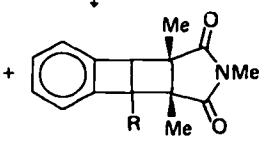


(Ref. 197) (122)



(Ref. 56b) (123)



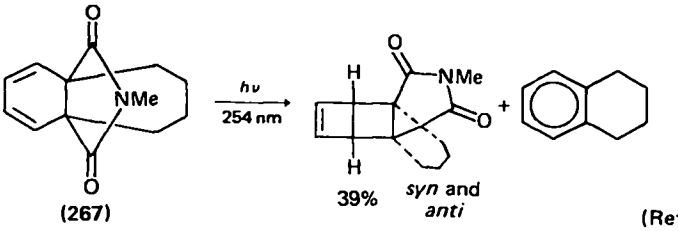


(Ref. 198) (124)

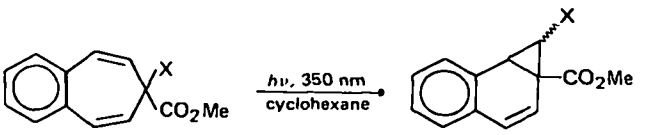
R = Ph (3.5%)
R = H (30%)

R = Ph (23%)

R = Ph (28%)
R = Me (71%)
R = H (10%)



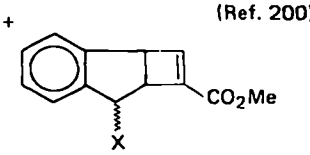
(Ref. 199) (125)



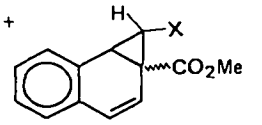
(270-h) (X = H)
(270-d) (X = D)

(271-h) (51%)
(271-d) (27%)

(Ref. 200) (126)

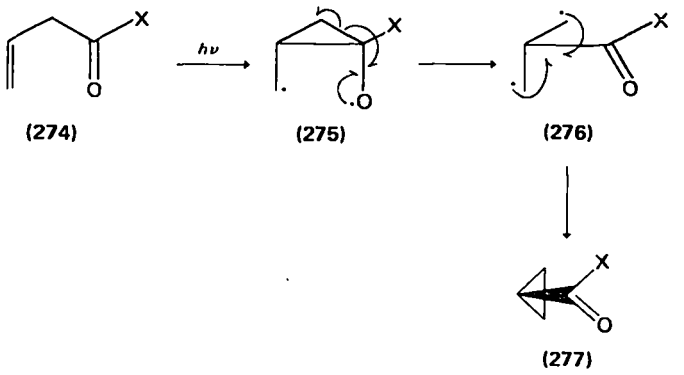


(272-h) (14%)
(272-d) (5%)



(273-h) (35%)
(273-d) (67%)

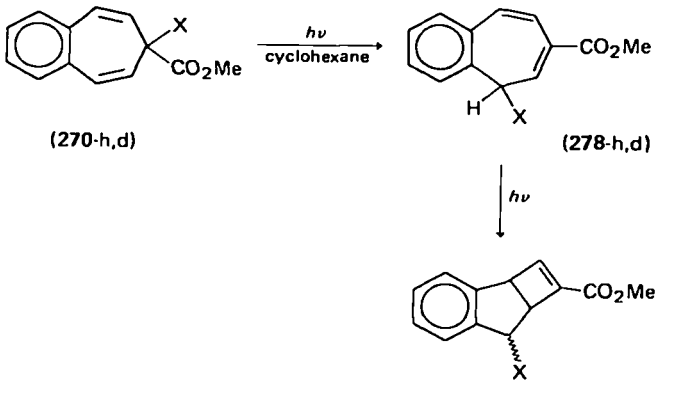
For the methyl and ethyl esters of Feist's acid (**261**), the initial photochemical process is probably homolytic cleavage of the cyclopropane bond to yield the diester of trimethylene methane (**262**). This common intermediate then partitions among the four identified products[197]. Dihydrophthalimide (**99**) and analogues **264** and **267** (equations 123–125) each undergo a 1,2-acyl migration of the imide function, resulting in a new cyclopropyl imide (**100**, **266** and **269**, respectively). This skeletal rearrangement is suggestive of the oxa-di-π-methane process for β,γ-unsaturated ketones[117,145,146,201], formulated in equation (137), and at least one author[198] has invoked this mechanism. However, Fuchs[56b] suggests a *type I* cleavage reaction, analogous to the ketone *type I* α-cleavage reaction, followed by recombination (shown in equation 123).



(274) (275) (276) (277) (127)

Examples of β,γ-unsaturated ester rearrangements such as those of the benzotropilidenes (shown in equation 126) may also be viewed as analogous to oxa-di-π-methane rearrangements. Swenton has found that the carbomethoxy group can compete with hydrogen for the 1,7 suprafacial migration to form **273** and **271** (X = H), respectively[200]. 7,7-Dicarbomethoxy-3,4-benzotropilidene (**270**, X = CO_2Me) rearranges on photolysis to benzonorcaradiene (**271** ≡ **273**) as the only product in very high efficiency ($\Phi = 0.78$)[200a].

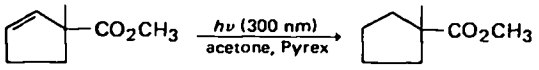
In examining the mechanism for the formation of the cyclobutene product **272**, Swenton and Madigan[200c–e] irradiated 1-deuterio-1-carbomethoxy-3,4-benzotropilidene (**270**, X = D) and obtained the deuterium distribution indicated in equation (126), X = D. The deuterium distribution in the products reveals that at least three pathways are followed by the excited benzotropilidene: (*i*) a 1,7-hydrogen (deuterium) migration followed by a thermal electrocyclization to norcardiene **271**, (*ii*) a 1,7-carbomethoxy migration (a vinylogous oxa-di-π-methane rearrangement?) followed by a thermal electrocyclization to norcardiene **273** and (*iii*) an unusual 1,3-hydrogen migration followed by a photochemical electrocyclization of the diene to cyclobutene **272**. Independent examination of the photochemistry of 5-carbomethoxy-1,2-benzotropilidene (**278**) showed that it proceeded quantitatively to the cyclobutene ester **272** under the reaction conditions used for **270** (equation 128). Most intriguing was the kinetic isotope effect found for the rearrangement of **270** to **271**. A value of 3.6 for k_H/k_D was calculated from the



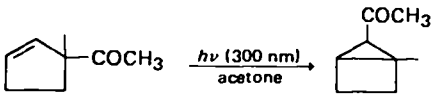
(270-h,d) (278-h,d) (272-h,d) (128)

relative efficiencies for formation of **271**-h vs d ($\Phi = 0.38/0.21$), assuming that the rate of carbomethoxy migration is identical for labelled and unlabelled tropilidene [**270**-h vs d, $(\Phi_{app})_{rel} = 0.20/0.40$]. The overall rearrangement efficiencies for both tropilidenes are nearly constant [$(\Phi_{dis})_{rel} = 1.00, 300$ nm] and high ($\Phi \cong 0.6$). Furthermore, acetophenone sensitization was not productive and the lack of quenching confirmed the singlet multiplicity for these rearrangements lending credence to the assumptions invoked in obtaining the isotope effects[200c].

Although these photoreactions involve a skeletal rearrangement which is consistent with the oxa-di-π-methane migrations of ketones. experimental evidence does not support this analogy. First, the multiplicity of the ketone reaction is generally found to be triplet[145,146,201], whereas the ester and imide reactions are singlet rearrangements. Second, attempts have failed[202] to induce an oxa-di-π-methane rearrangement (equation 127, X = OR) for esters that are simply β,γ-unsaturated chromophores and have direct structural correspondence with ketones that are known to undergo the oxa-di-π-methane reaction[203] (compare equations 129 and 130). For example, under conditions where 3-acetyl-3-methylcyclopentene (**281**) rearranges to 5-acetyl-1-methylbicyclo[2.1.0]pentane (**282**) with an efficiency of 0.11[203], the methyl ester **279** fails to react[202]. Only a trace of the reduced ester **280** along with dimeric and polymeric material, was obtained from irradiation of an acetone solution of ester **279**[202].



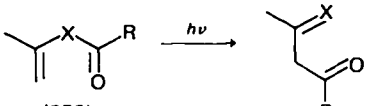
(279) (280) <10% (129)



(281) (282) 65% (130)

These carbonyl migration reactions will require additional study in order to delineate the scope and mechanism for each type of rearrangement found.

A second rearrangement reaction frequently encountered for β,γ-unsaturated ketones is the 1,3-acyl migration shown in equation (131), X = CR_2. For enol esters (X = O) and acyl enamines (X = NR), this photorearrangement is commonly referred to as a photo-Fries reaction[11,20]. Many examples of these 1,3-acyl migrations

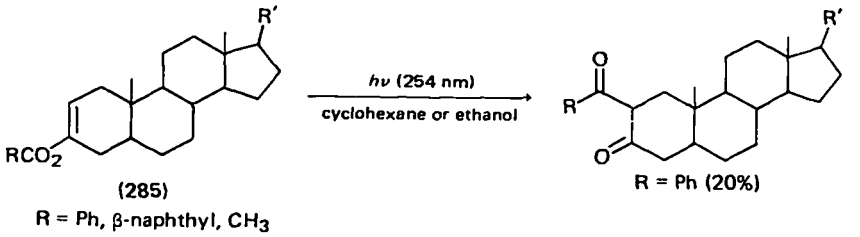


(283) (284) (131)

X = CR_2, O, NR

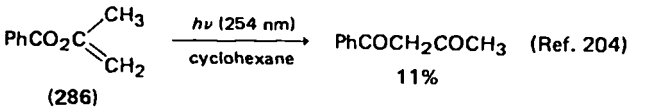
have been reported[33a,c, 204-206], of which only a few are listed in equations (132)–(136)

In many instances the reactions have been found to be reversible, as indicated. Generally, the diketone is the more photolabile, particularly for α-disubstituted-β-diketones (note equations 134 and 136 where a photoequilibrium was reached).



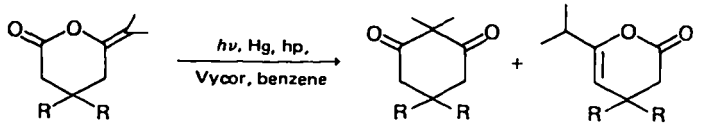
(285)
R = Ph, β-naphthyl, CH_3

(Ref. 204, 33a) (132)



(286)

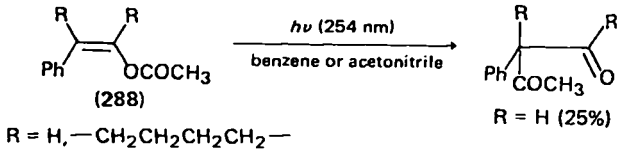
(Ref. 204) (133)



(287)
R = H, CH_3

3% 2%

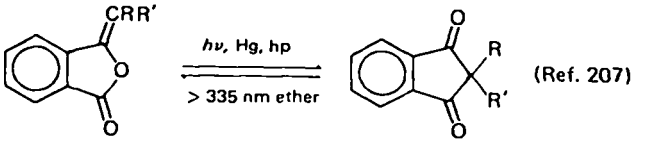
(Ref. 206) (134)



(288)
R = H, $-CH_2CH_2CH_2CH_2-$

R = H (25%)

(Ref. 205) (135)

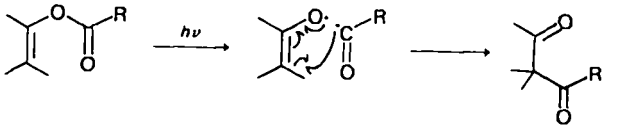


(289)
R = Ph
R' = CH_3

9%

(Ref. 207) (136)

The mechanism of the migration reaction probably involves a *type I* cleavage followed by recombination of the acyl radical at the α-carbon (equation 137), analogous to one of the mechanisms postulated for ketone 1,3-migrations. An

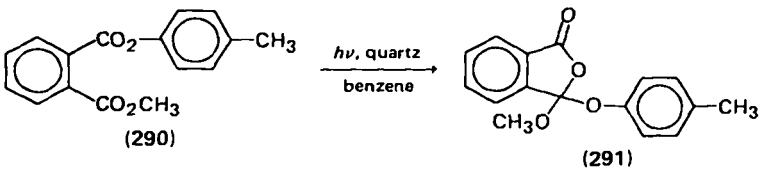


(137)

important side-reaction that often accompanies 1,3-acyl migrations is decarbonylation. Libman, Sprecker and Mazur[28] found exclusive decarbonylation when enol trichloroacetates were irradiated (see Section III.A) in accord with what would be expected from a *type I* cleavage mechanism.

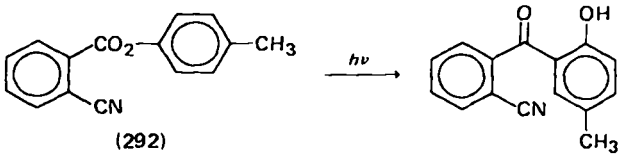
Recently, the study of steroidal enol acetates **285** (R = Ph, β-naphthyl and 2-anthryl) revealed a wavelength dependence for the rearrangement. The 2-anthryl derivative photorearranged only with 254 nm and not with 366 nm irradiation. Since singlet-state reactivity was established, the wavelength dependence was interpreted as an effect of energy available for the bond-breaking processes. Furthermore, from the lack of any side-reactions (such as decarbonylation, aldehyde formation or radical coupling) even at high conversons (90%), the suggestion was advanced that either the rearrangement is concerted (one-step) or that the radical pair is in a tight cage[204c].

Kende and Belletire[208] observed a *type I* process which produced the ortho anhydride **291** in 20% yield from the phthalate ester **290** (equation 138). Again,



(290) (291) (138)

singlet reactivity was established through the lack of sensitization by benzophenone. This reaction, which was to have been a key step in Kende's synthesis of Daunomycin[209], failed to give the desired photo-Fries product. However, the abnormal product **291** can be avoided if the carbomethoxy group is replaced by a cyano substituent, as in **292**, for which the normal photo-Fries rearrangement is observed[208] (equation 139).



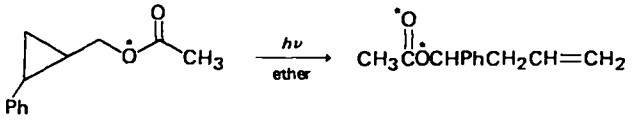
(292) (139)

The rearrangements discussed in this section illustrate the variety of reactions currently known to proceed photochemically. Systematic investigation of these reactions and the exploration of new rearrangements remains to be done.

B. Photosolvolysis

The question of whether homolytic or ionic bond-breaking processes occur as primary processes from the excited states of esters and other carboxylic acid derivatives has plagued investigators for two decades. Evidence for cation[7,15,123,132,210] and for radical intermediates[75,120,124,128,130,135,142] has been gathered in these photosolvolysis reactions. From identification of the behaviour of the intermediates, the excited-state reaction is formulated as either homolytic or heterolytic C—O bond cleavage. However, little direct evidence is available which will allow the formulation of a reaction sequence from initial excitation to the final product for photosolvolysis reactions.

Examples of the methods employed for determining the nature of the intermediates include flash photolysis (where both radicals[75] and carbonium ion[210] intermediates have been observed), oxygen-18 labelling experiments[132,211] (e.g. carbonium ion rearrangements have been observed[211], equation 140), and stereochemical probes[212]. Levi and Malament[212] irradiated a series of *meso* and *d,l*-di-

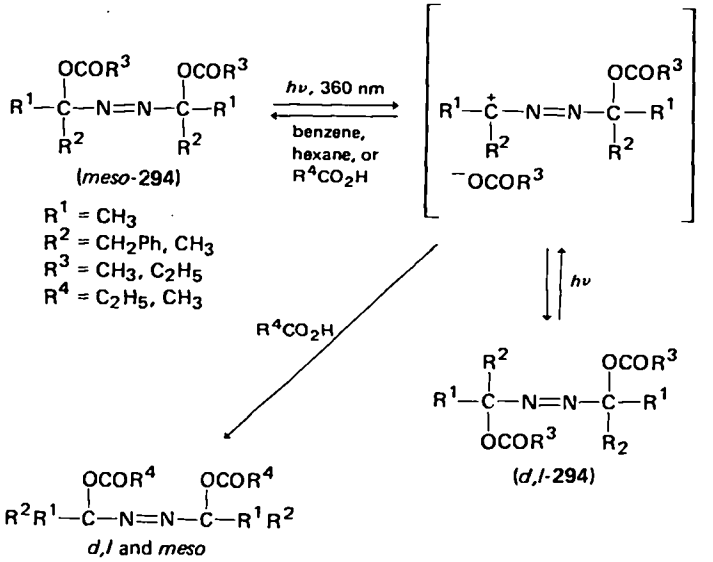


(140)

(293)

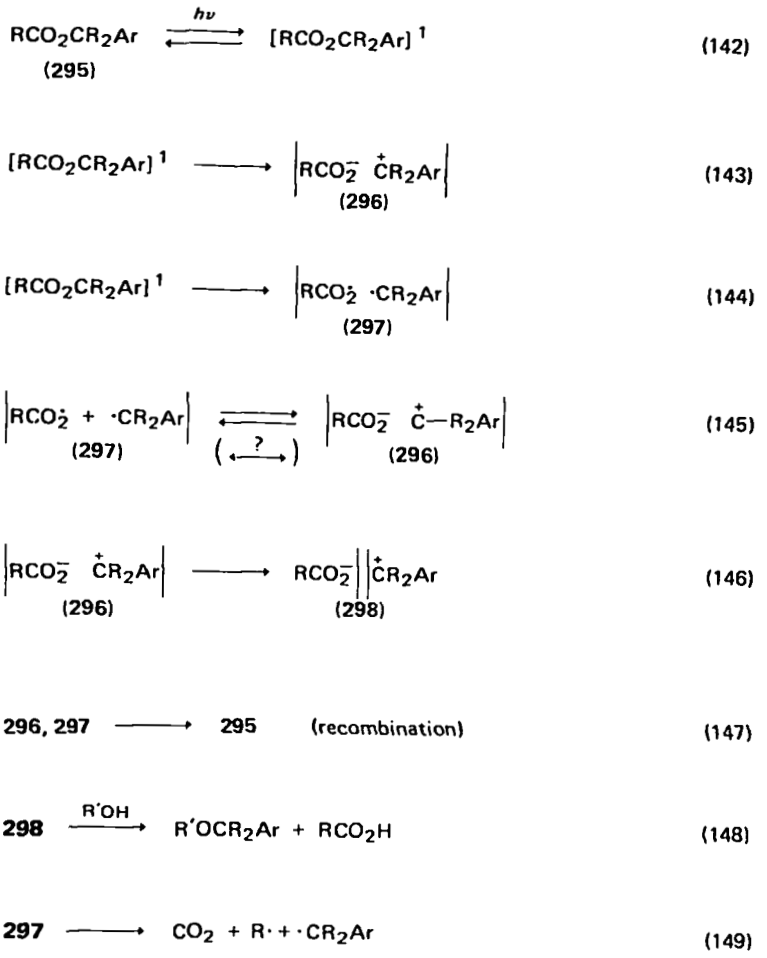
*Indicates ^{18}O

acyloxyazo derivatives (**294**, equation 141) and found that a highly efficient stereoequilibration occurred from the singlet state of **294**. Exchange of the acyloxy groups as well as the stereochemical exchange clearly points to a carbonium-ion intermediate in this reaction. Interestingly, the equilibration readily occurred in both polar and non-polar solvents[212].



(141)

For the acyloxyazo derivatives and the previous examples of photosolvolysis reactions (see also Section II, equation 12–14 and Section III.A), the absorbing chromophore is usually an aryl group or another unsaturated functionality such as an azo group. For many of these chromophores, the first excited singlet is the reactive state and can have significant ionic character. Heterolytic cleavage of the bond to the acyl oxygen forms an ion pair (Scheme 9, equation 143). Alternatively, the reaction could occur via homolytic bond breaking followed by electron transfer (equations 144 and 145) to form the same ion pair (Scheme 9). Whether **297** and **298** exist as separate species or are contributors to a resonance hybrid is dependent on the nature of the substituents and the proximity of the two fragments. A mechanism similar to Scheme 9 has been postulated earlier[213,142,130,135]. For at least one reaction, the photodecarboxylation and oxygen scrambling in phenyl-



SCHEME 9.

acetates such as **154**, **160** and **164** and lactone **151**, the interconversion of diradical and zwitterionic intermediates has been ruled out[130,135] (Scheme 9, equation 145). The controlling factors are (*i*) the differences in electron affinity (EA) and ionization potential (IP) of the two fragments, (*ii*) the solvent polarity, (*iii*) the energy available in the excited singlet state and (*iv*) the intersystem crossing efficiency. Thus, for large (EA–IP) values, both electron transfer and heterolytic cleavage to **296** would be favoured. Likewise, high solvent polarity will favour ion formation[195b]. Finally, the excited singlet must possess enough energy to cleave the bond and must have a lifetime long enough for that process to compete with other photophysical and photochemical reactions. If intersystem crossing competes effectively, then the reaction takes on radical character from the triplet state[213,142].

Although this suggested mechanism has not been tested, it provides a basis upon which photosolvolysis reactions can be examined in the future. Further study, in progress in these laboratories as well as others, promises to solve some of the mysteries of these reactions.

VII. ACKNOWLEDGMENTS

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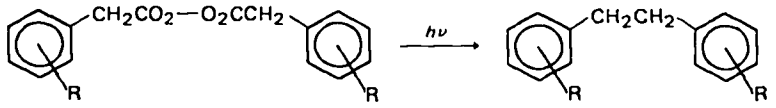
VIII. ADDENDUM

Since completion of the manuscript for this chapter, several reports have appeared which merit inclusion in this review. Also, reviews on the photochemistry of carboxylic acid derivatives are now available[214] and a recent monograph entitled *Photochemistry of Heterocyclic Compounds*, edited by Buchardt[215], contains several accounts of the functional group photochemistry discussed in this chapter. The additional reports included here are presented according to the section format used earlier.

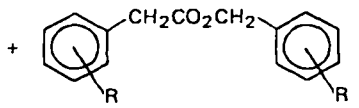
A. Decarbonylation (Section III)

o-Phenylene oxylate has been shown to quantitatively photodecarbonylate to *o*-phenylene carbonate[216]. The diester undergoes a *type I* α-cleavage reaction to a diradical which loses only one molecule of carbon monoxide before closure to the carbonate. No benzyne resulting from decarboxylation could be trapped in this the reaction conditions. After a three-hour irradiation, only the bibenzyl (~55%) and the ester (~35%) are present; the anhydride is completely converted to products.



(299a) R = *o*-MeO

(150)



(300a)

The studies by Roof and Cerfontain[57] have been extended to substituted phenylacetic anhydrides. When *o*-methoxy phenylacetic anhydride (**299a**) is photolysed (equation 150) and the reaction mixture examined at less than 30% conversion, approximately 10% of the reaction mixture is the ester **300a**[217]. After continued irradiation, beyond 40% conversion of the anhydride, the ester dis-

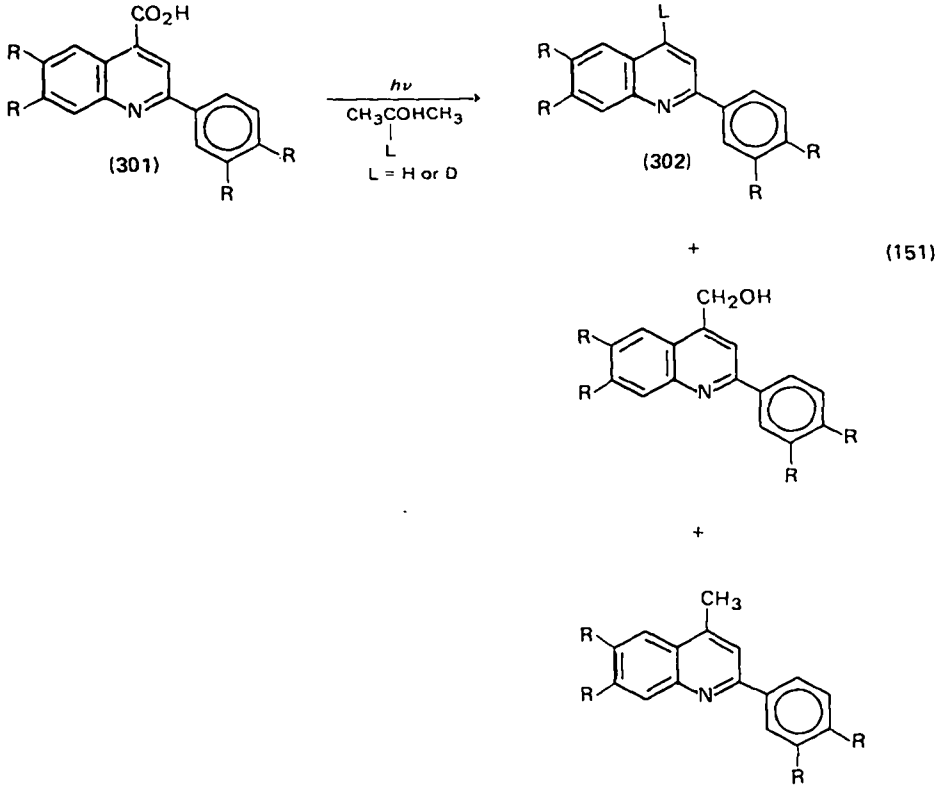
appears and none is found in the final reaction mixture. For the *p*-methoxy anhydride **299b**, the ester **154b** is formed in greater yield and is relatively stable to reaction. Analogous studies on phthaloyl peroxide[144] did produce benzyne (see Section IV).

The significance of this finding is the presence of ester photoproducts for these and other alkoxyphenyl anhydrides. Employing mixed anhydrides and the use of solvent effect studies have clearly indicated the intermediacy of the alkoxybenzyl carbonium ion. The pathway to their formation is not clear however; the authors suggest an electron-transfer step from the alkoxy aryl group to the carbonyl followed by homolytic cleavage[217].

B. Photodecarboxylation (Section IV)

Titanium-oxide catalysed photodecarboxylation of acetic acid[218] has been achieved in high yield with quantum efficiencies of 0.03 to 0.05. The major product is methane; the overall process is a photochemical reductive decarboxylation and complements the corresponding reactions of esters (see Section V.B). It appears that this reaction can be adapted to a larger scale and may be general for other carboxylic acids thus showing promise for synthetic applications. The mechanistic details are also discussed in this report.

Epling[219] has investigated the photodecarboxylation of quinoline-4-carboxylic acids (**301**). A radical mechanism is suggested by the finding that deuterium is



incorporated in **302** when the irradiation is carried out in 2-deuterio-2-propanol (equation 151). This reaction can be sensitized by Michler's ketone or xanthone and quenched by oxygen which establishes the triplet excited state as the reactive state.

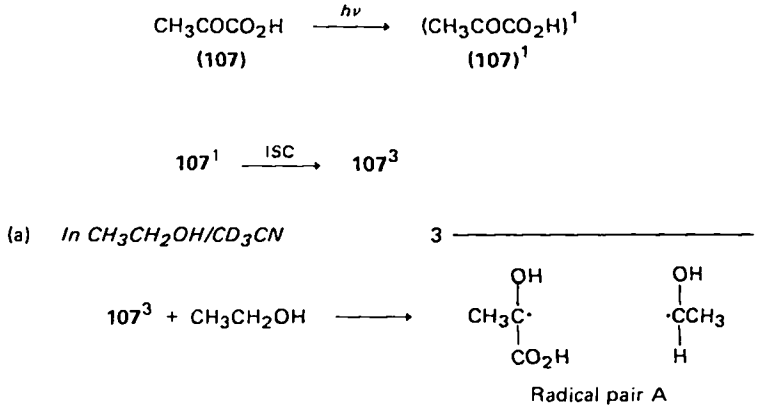
Studies employing CIDNP[220] and CIDEP[220b] on the photochemistry of pyruvic acid (**107**) have appeared. In an elegant study, Closs and Miller[200a] have shown that in hydrogen-atom donating solvents such as ethanol and 2-propanol, the n,π^* triplet state of pyruvic acid abstracts a hydrogen atom from solvent to form geminate radical pair A (Scheme 10). That geminate pair either couples to give *threo*- and *erythro*-2,3-dihydroxy-2-methylbutanoic acid (**303**), or disproportionates to give lactic acid and acetaldehyde or to the reactants (either directly or through the enol tautomer **304**). Free radicals from diffusion of the geminate pair out of the cage couple to form the dimethyltartaric acids.

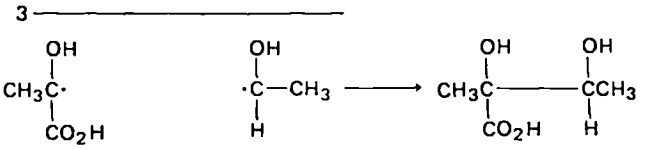
For concentrations of ethanol less than 0.5 M, a second geminate radical pair is generated by hydrogen abstraction from the initially formed acetaldehyde. The fact that acetaldehyde can compete with high concentrations of ethanol for the triplet of **107** implies a high reactivity of the aldehyde hydrogen. Coupling of geminate radical pair B gives 2-hydroxy-2-methylacetoacetic acid (**305**), not reported in previous studies. The thermal decarboxylation of **305** is the major path to acetoin.

A similar radical-pair mechanism operates in D_2O and acetonitrile. As illustrated in Scheme 10 (b), the initial step in these solvents is *type I* cleavage of the ketone carboxyl bond to yield geminate radical pair C. This pair is the source of acetaldehyde and CO_2 by disproportionation. Alternatively, **107** can serve as a hydrogen atom acceptor from carboxyl radicals that escape the cage pair. The radical thus generated, CH_3COHCO_2H, combines with acetyl radicals to give the same acetoacetic acid **305** found in other solvents. Thermal decarboxylation provides the route to acetoin as indicated above. *This pathway rather than the carbene mechanism postulated by Leermakers*[62,63a–c] *would appear to be more likely.*

Closs and Miller[220a] have demonstrated the power of CIDNP in the study of radical mechanisms. Each of the molecules listed in Scheme 10 was observed to give either a net effect or a multiplet effect which reflected its origin in terms of the

SCHEME 10. Radical-pair mechanism for the photochemistry of pyruvic acid (**107**). Hydrogen-exchange reactions and diffusion of radicals from geminate caged pairs are not shown.





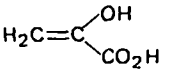
threo- and *erythreo*-(303)

+

$CH_3CHOHCO_2H + CH_3CHO$

Lactic acid

+



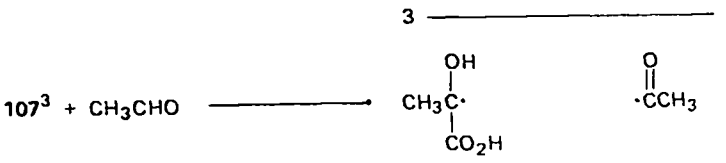
$+ CH_3CH_2OH$

(304)

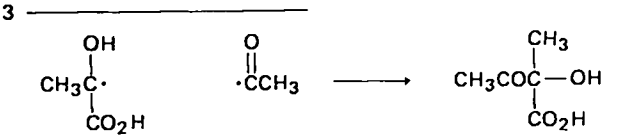
+

$CH_3COCO_2H + CH_3CH_2OH$

(107)

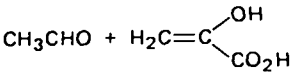


Radical pair B



(305) 30%

+

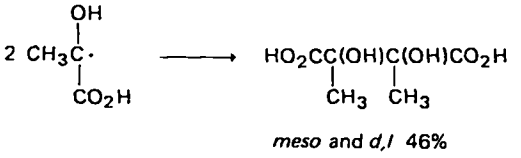


(304)

+

$CH_3CHO + CH_3COCO_2H$

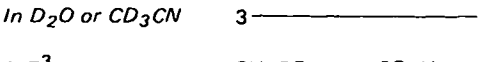
(107)



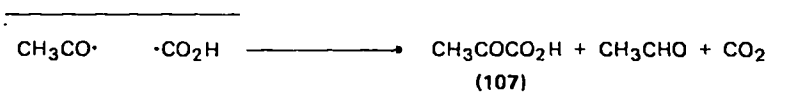
meso and *d,l* 46%

Acetoin

(b) *In D_2O or CD_3CN*

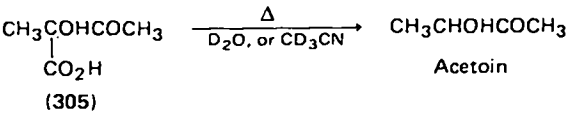


Radical pair C



(107)

(305)



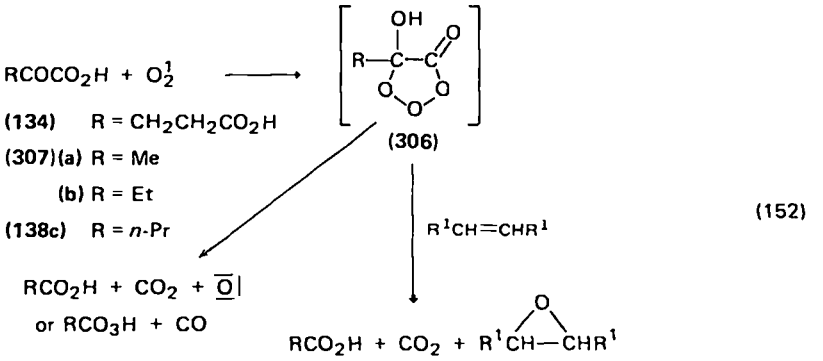
(305)

Acetoin

excited state and radical precursors. It is indeed impressive that such an array of complex steps can be so clearly established by this technique and by a judicious choice of experimental conditions.

The role of singlet oxygen during the dye-sensitized photodecarboxylation of α-ketoglutaric acid (**134**) and other α-keto carboxylic acids (**138**) continues to

receive attention. Recent communications by Jefford and coworkers[221a] and Moriarty and coworkers[221b] detail the role of singlet oxygen in the photochemistry of **134**. There are apparently two pathways by which **134** can decarboxylate: (a) singlet oxygen-induced decomposition originally suggested by Jefford[104] and (b) decarboxylation of **134** by direct triplet sensitization by the dye (methylene blue) as suggested by Davidson[90]. Moriarty[221b] generated singlet oxygen from triphenyl phosphite–ozone adducts and by microwave discharge to obtain 24–30% yields of succinic acid. Furthermore, he was able to show that an intermediate (e.g. **306**) is generated which is capable of transferring an oxygen atom to an alkene (equation 152). The role of **306** as a model for the intermediate in



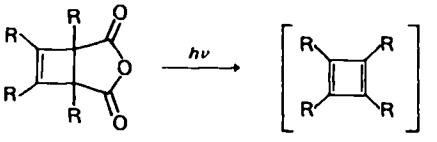
α-ketoglutarate-dependent oxygenases, a ground-state oxygen-transfer reaction, is also suggested.

While singlet oxygen is not required for efficient decarboxylation of α-ketoglutaric acid, it is necessary for efficient decarboxylation of the related α-keto monocarboxylic acids **307** and **138c**[221a]. Yields range from 50–100% of the decarboxylated acids (equation 152) and, in one example, peroxybutyric acid was isolated from oxovaleric acid (**138c**).

In connection with Chapman's earlier isolation and spectral analysis of cyclobutadiene (**180**) by photodecarboxylation of β-lactone **156**[125], recent evidence from Masamune's group[222] suggests that the molecule possesses a symmetry lower than D_{4h}. Two additional infrared bands of very low intensity were detected using FT–IR. Though not established, the rectangular geometry (D_{2h}) would be in accord with this latest observation and with the inability to detect an e.s.r. signal expected from a triplet square planar ground state of **180** and its analogues. Furthermore, a number of theoretical studies on **180** have shown that the singlet reactangular geometry (D_{2h}) is about 10 kcal/mol lower than the triplet square planar (D_{4h}) structure[223].

In addition to generating **180** from the β-lactone **156**, Masamune employed an anhydride route, developed earlier by Maier[224] and by Lemal[225], shown in equation (153). This alternative method provides the cyclobutadiene from a decarbonylation–decarboxylation process in excellent yield (41% for the tetrafluoro derivatives, **180b**[225]).

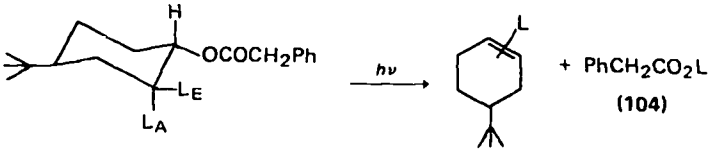
Finally, the extensive studies of Roof and Cerfontain included a reexamination of the photodecarboxylation reactions of substituted benzyl phenylacetates 154a–i[217]. The conclusions that radical mechanisms dominate this series (as discussed earlier in Section IV) were reaffirmed.



R = H, D, F (180)(a) R = H, D (b) R = F (153)

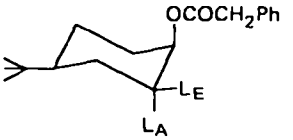
C. Hydrogen Abstraction by Carboxyl Oxygen (Section V)

Conformationally biased cyclohexyl phenylacetates **308a–d** have been examined for *syn* and *anti type II* elimination reactions by Eadon and coworkers[226]. The reaction (equation 154) was monitored by the appearance of phenylacetic acid (**104**)



(308)(a) L_E = D, L_A = H
(b) L_E = H, L_A = D

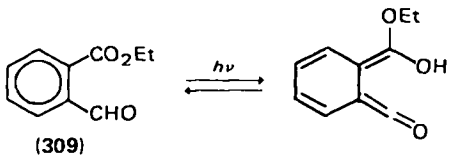
(154)



(308)(c) L_E = D, L_A = H
(d) L_E = H, L_A = D

and the analysis of *syn* or *anti* elimination was based on the deuterium content for **104**. The ratios of **104**-H/**104**-D from the four esters were 3.9, 8.4, 1.6 and >50 (for **308b** a–d, respectively). The surprisingly high value for the ratio from **308b** indicated that *trans* elimination may predominate for the equatorial esters **308a** and **b** in contrast to the *cis* elimination suggested by Yarchak, Dalton and Saunders[168].

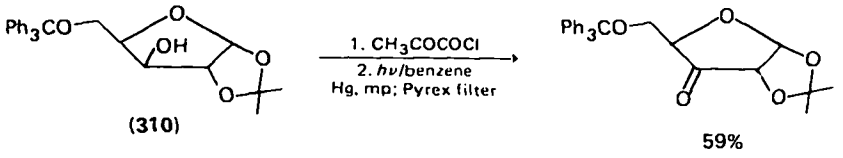
A *type II* elimination from ethyl acetate has been accomplished by multiphoton absorption from a high-energy infrared pulsed CO_2 laser[227]. The H_2C–OCO bond was irradiated but redistribution of the energy to other bonds was postulated to account for the fact that a relatively clean *type II* elimination of ethylene followed. Future studies are expected to probe the nature of this reaction.



(309) (155)

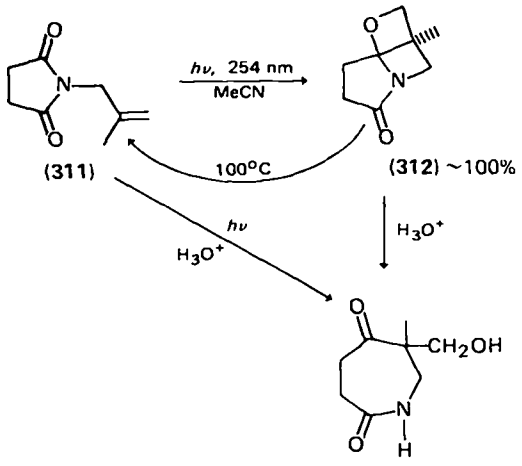
Several examples of intramolecular hydrogen atom abstractions by an ester carbonyl group have appeared[228]. Equation (155) illustrates the facility with which aldehydic hydrogens can be abstracted[228c]. Solvent isotope exchange and trapping studies were used to establish this as the primary photochemical process for **309**.

Binkley[229] has used the hydrogen abstraction process from pyruvate esters as a very effective method for oxidation of sensitive alcohols (nucleosides and carbohydrates). Equation (156) illustrates the method including the yield of isolated oxidation product. These varied from 38% to 80% for the combined steps.



(310) 59% (156)

Work on *N*-substituted imides and phthalimide derivatives[235] has shifted to alkene derivatives[230]. Oxetane formation (**312**) occurs rather than hydrogen abstraction for the imides[230a] (equation 157). In acidic methanol or water, the oxetanes lead to ring-expanded products (e.g. **313**) as found with the alkyl-substituted phthalimides.

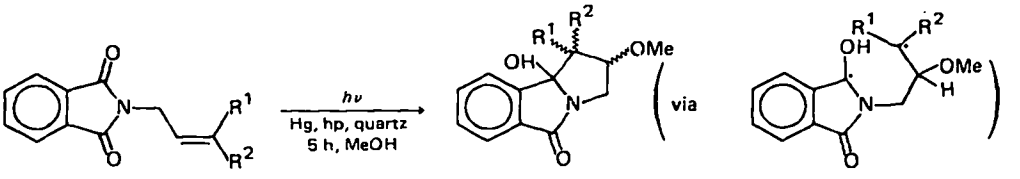


(311) (312) ~100% (157)

(313)

For phthalimides, an ionic mechanism is invoked to explain the formation of the methanol-addition cyclized products found in the photolysis of **314a–c**[230b] (equation 158). Initial electron transfer from the alkene to the phthalimide moiety followed by methanol addition would generate diradical **316** which then closes to the tricyclic amide **315**. Mazzocchi[231] has accomplished a similar ring-expansion for *N*-methyl phthalimide by intermolecular cycloaddition of butadiene.

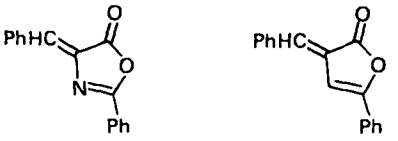
Finally, a reexamination by Sakuragi, Ono, Hata and Takumaru[232] of the wavelength dependence in the photochemistry of **225** and **247** has shown that the orbital overlap mechanism suggested by Ullman is in error[180]. The sensitizer selectivity for photoisomerization and hydrogen-atom abstraction reactions of



(314)(a) $R^1 = R^2 = Me$
(b) $R^1 = H$, $R^2 = Me$
(c) $R^1 = H$, $R^2 = Ph$

(315a–c) (316) (158)

lactones 225 and 247 has shown that the lack of selectivity is a result of reabsorption of sensitizer fluorescence by the oxazolone 225. Those sensitizers which are 'selective' do not emit fluoresence in the wavelength region necessary to generate the upper excited state responsible for hydrogen-atom abstraction. These sensitizers are, in fact, selective for triplet energy transfer to the lowest-lying triplet (π,π^*) of 225 which leads exclusively to $Z-E$ isomerization. Other sensitizers such as naphthalene and fluorene emit fluorescence which is reabsorbed by 225 leading to the

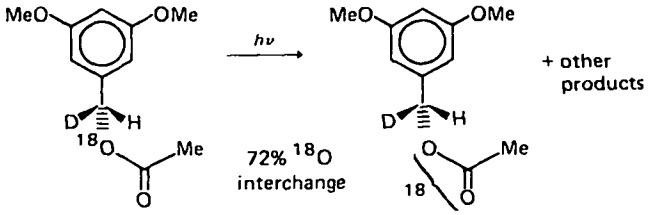


(225) (247)

hydrogen-atom abstraction reaction and transfer triplet energy to 225 resulting in the $Z-E$ isomerization. It would appear that the entire mechanistic picture is clouded and that further work is needed.

D. Photorearrangements and Photosolvolysis Reactions (Section VI)

Jaeger[233] has reexamined the photochemistry of 3,5-dimethoxybenzyl acetate (11) reported earlier[132]. Utilizing ^{18}O-labelled optically active ester 11, Jaeger has shown that the recovered ester has undiminished optical activity but 72% oxygen-18 interchange (equation 159), a result in accord with studies in the unsubstituted benzyl series, i.e., *S*-(−)-164.



(159)

(11)

The photosolvolysis of substituted benzyl acetates continues to attract interest. Additional studies by Roof and Cerfontain[217] and Holmstead and Fulmer[234] have appeared, but the detailed mechanism and the reaction parameters appear to be as elusive as ever.

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